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(54) Title: NOVEL SECRETED PROTEINS AND THEIR USES

(57) Abstract: The present invention provides nucleic acid sequences encoding novel human proteins. These novel nucleic acids are useful for constructing the claimed DNA vectors and host cells of the invention and for preparing the claimed nucleic acids, recombinant proteins and antibodies that are useful in the claimed methods and medical uses.

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NOVEL SECRETED PROTEINS AND THEIR USES**FIELD OF THE INVENTION**

This application claims priority of Provisional
5 Applications Serial No. 60/224,642 filed August 11, 2000,
and Serial No. 60/241,779 filed October 19, 2000.

The present invention relates to the identification
and isolation of novel DNA, therapeutic and drug discovery
uses, and the recombinant production of novel secreted
10 polypeptides, designated herein as LP105, LP061, LP224,
LP240, LP239(a), LP243(a), LP243(b), LP253, LP218,
LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244,
LP186, LP251(b), LP255(b), and LP223(b). The present
invention also relates to vectors, host cells, and
15 antibodies directed to these polypeptides.

BACKGROUND OF THE INVENTION

Extracellular proteins play an important role in the
formation, differentiation and maintenance of multi-
20 cellular organisms. The fate of many individual cells,
e.g., proliferation, migration, differentiation, or
interaction with other cells, is typically governed by
information received from other cells and/or the immediate
environment. This information is often transmitted by
25 secreted polypeptides (for instance, mitogenic factors,
survival factors, cytotoxic factors, differentiation
factors, neuropeptides, and hormones) which are, in turn,
received and interpreted by diverse cell receptors or
membrane-bound proteins. These secreted polypeptides or
30 signaling molecules normally pass through the cellular
secretory pathway to reach their site of action in the
extracellular environment.

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Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

The present invention describes the cloning and characterization of novel proteins, termed LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), and LP223(b), as well as active variants and/or fragments thereof.

SUMMARY OF THE INVENTION

The present invention provides isolated LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), and LP223(b) polypeptide encoding nucleic acids and the polypeptides encoded thereby, including fragments and/or specified variants thereof. Contemplated by the present invention are LP probes, primers, recombinant vectors, host cells, transgenic animals, chimeric antibodies and constructs, LP polypeptide antibodies, as well as methods of making and using them diagnostically and therapeutically as described and enabled herein.

The present invention includes isolated nucleic acid molecules comprising polynucleotides that encode LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244,

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LP186, LP251(b), LP255(b), and LP223(b) polypeptides as defined herein, as well as fragments and/or specified variants thereof, or isolated nucleic acid molecules that are complementary to polynucleotides that encode such LP polypeptides, or fragments and/or specified variants thereof as defined herein.

A polypeptide of the present invention includes an isolated LP polypeptide comprising at least one fragment, domain, or specified variant of at least 90-100% of the contiguous amino acids of at least one portion of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38.

The present invention also provides an isolated LP polypeptide as described herein, wherein the polypeptide further comprises at least one specified substitution, insertion, or deletion corresponding to portions or specific residues of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38.

The present invention also provides an isolated nucleic acid probe, primer, or fragment, as described herein, wherein the nucleic acid comprises a polynucleotide of at least 10 nucleotides, corresponding or complementary to at least 10 nucleotides of SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37.

The present invention also provides compositions, including pharmaceutical compositions, comprising an LP polypeptide, an LP polypeptide-encoding polynucleotide, an LP polynucleotide, and/or an LP polypeptide antibody, wherein the composition has a measurable effect on an activity associated with a particular LP polypeptide as disclosed herein. A method of treatment or prophylaxis based on an LP polypeptide associated activity as disclosed

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herein can be effected by administration of one or more of the polypeptides, nucleic acids, antibodies, vectors, host cells, transgenic cells, and/or compositions described herein to a mammal in need of such treatment or

5 prophylactic. Accordingly, the present invention also includes methods for the prophylaxis or treatment of a patho-physiological condition in which at least one cell type involved in said condition is sensitive or responsive to an LP polypeptide, LP polypeptide-encoding

10 polynucleotide, LP nucleic acid, LP polypeptide antibody, host cell, transgenic cell, and/or composition of the present invention.

The present invention also provides an article of manufacture comprising a container, holding a composition

15 effective for treating a condition disclosed herein, and a label.

The present invention also provides a method for identifying compounds that bind an LP polypeptide, comprising:

20 a) admixing at least one isolated LP polypeptide as described herein with a test compound or composition; and

b) detecting at least one binding interaction between the polypeptide and the compound or composition, optionally further comprising detecting a change in

25 biological activity, such as a reduction or increase.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Applicants have identified cDNA clones comprising polynucleotides that encode novel polypeptides or novel

30 variants of known polypeptides:

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1) LP105

LP105 polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:1 are contemplated as one
5 embodiment of the present invention. Specifically, polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:2, as well as fragments, variants, and derivatives thereof. Accordingly, LP105 polynucleotides encoding the LP105 polypeptides of the
10 present invention are also contemplated by the present invention. LP105 polynucleotides are predominantly expressed in prostate and kidney tissues.

The LP105 polypeptide as shown in SEQ ID NO:2 shares sequence similarity with a recently reported human lefty
15 protein (WO 99/09198). Lefty proteins are members of the TGF-beta family and two LEFTY genes, LEFTY A and B, have been localized by FISH to 1q42, a region syntenic to the location to which the mouse Lefty genes have been mapped at 1H5 [Kosaki, et al., *Am. J. Hum. Genet.* 64(3):712-21 (1999);
20 Meno, et al., *Genes Cells* 2(8):513-24 (1997)]. LEFTY A is identical to EBAF [Kothapalli, et al., *J. Clin. Invest.* 99(10):2342-50 (1997)]. Analysis of 126 human cases of L-R axis malformation showed a single nonsense and a single missense mutation in the LEFTY A gene. Both mutations lay in
25 the cysteine-knot region of the LEFTY A protein and the phenotype of affected individuals was very similar to that typically seen in Lefty-1 $-/-$ mice with L-R axis malformations. Furthermore, the LP105 polypeptide as shown in SEQ ID NO:2 shares sequence similarity with human bone
30 morphogenic protein 18 (WO 99/29718). Compositions comprising LP105 polypeptides, polynucleotides, and/or antibodies are useful for the treatment of defects in or

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wounds to tissues including, but not limited to, epidermis, nerve, muscle, cardiac muscle, and organs including, but not limited to liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney. Furthermore, compositions comprising

5 LP105 polypeptides, polynucleotides, and/or antibodies can be useful for modulating sexual development, pituitary hormone production, hematopoiesis, wound healing, tissue repair, and the formation of bone and cartilage.

Compositions comprising LP105 polypeptides, polynucleotides,

10 and/or antibodies can also be used to treat such conditions as cancer including, but not limited to prostate and kidney cancer, interstitial lung disease, infectious diseases, autoimmune diseases, arthritis, leukemia, lymphomas, immunosuppression, immunity, humoral immunity, inflammatory

15 bowel disease, myelosuppression, periodontal disease, osteoarthritis, osteoporosis, and other abnormalities of bone, cartilage, muscle, tendon, ligament, meniscus, and/or other connective tissues as well as dysfunctional growth and differentiation patterns of cells.

20

2) LP061

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:3 are

25 contemplated by the present invention. Specifically, polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:4, as well as fragments, variants, and derivatives thereof. Accordingly, LP061 polynucleotides encoding LP061 polypeptides of the present

30 invention are also contemplated by the present invention. LP061 polynucleotides are predominantly expressed in diseased thyroid. The present invention includes a human

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nucleotide sequence (Incyte clone 2719035H1) as shown in SEQ ID NO:3 which appears to be a shortened splice-variant of the published human fukutin nucleotide sequence (GenBank AB008226).

5 Fukuyama-type congenital muscular dystrophy (FCMD), one of the most common autosomal recessive disorders in Japan (incidence is 0.7 to 1.2 per 10,000 births), is characterized by congenital muscular dystrophy, in conjunction with brain malformation (micropolygia). The

10 FCMD gene was mapped to a region of less than 100 kilobases which included the marker locus D9S2107 on human chromosome 9q31. The mutation responsible for FCMD is a retrotransposal insertion of tandemly repeated sequences within this candidate-gene in all FCMD chromosomes carrying the founder

15 haplotype (87%). The inserted sequence is about 3 kilobases long and is located in the 3' untranslated region of a gene encoding a new 461 amino acid protein. This novel gene, termed fukutin, is expressed in heart, brain, skeletal muscle, pancreas and lymphoblasts in normal individuals, but

20 not in FCMD patients who carry the insertion. Two independent point mutations confirm that mutation of this gene is responsible for FCMD. The predicted fukutin protein contains an amino-terminal signal sequence and one glycosylation site, which together with results from

25 transfection experiments suggests that fukutin is a secreted protein. Abnormalities in basal lamina in FCMD muscle and brain have been seen by electron microscopy [Nakano, et al., *Acta Neuropathol.* 91(3):313-21 (1996); Ishii, et al., *Neuromuscul. Disord.* 7(3):191-7 (1997)]. Therefore it has

30 been suggested that secreted fukutin may be associated with the extracellular matrix surrounding expressing cells where it forms a complex with other extracellular components to

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stabilize a microenvironment supportive for normal cellular/tissue function. In muscle, fukutin complexes might stabilize the function of muscle fibers/sarcomeres; in brain, fukutin may assist the migration of neuronal

5 precursors during cortical development [Fukuyama, et al., *Brain Dev.* 3(1):1-29 (1981)].

Accordingly, compositions comprising LP061 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases,
10 disorders, and/or conditions including, but not limited to, brain malformation (micropolygria), Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, ALS, muscular pathologies including, but not limited to, muscular dystrophies including, but not limited
15 to, congenital muscular dystrophies such as fukuyama-type congenital muscular dystrophy, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia,
20 paranoia, obsessive compulsive disorder, panic disorder learning disabilities, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

25 **3) LP224**

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:5 are contemplated by the present invention. Specifically,
30 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:6, as well as fragments, variants, and derivatives thereof. Accordingly, LP224

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polynucleotides encoding LP224 polypeptides of the present invention are also contemplated by the present invention.

The gene encoding the LP224 polypeptide has been localized to chromosome 4p16 (GenBank hit g7022852) and the LP224 polypeptide as shown in SEQ ID NO:6 shares sequence similarity with a protein encoded by the leucine-rich, glioma inactivated 1 tumor suppressor gene. LGI1 has the highest homology with a number of transmembrane and extracellular proteins which function as receptors and adhesion proteins. LGI1 is predominantly expressed in neural tissues, especially in brain; its expression is reduced in low grade brain tumors and it is significantly reduced or absent in malignant gliomas. Its localization to the 10q24 region, and rearrangements or inactivation in malignant brain tumors, suggest that LGI1 is a candidate tumor suppressor gene involved in progression of glial tumors [Chernova, et al., *Oncogene* 17(22):2873-81 (1998)]. Accordingly, compositions comprising LP224 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of bipolar affective disorder [Ewald, et al., *Mol. Psychiatry* 3(5):442-8 (1998)], hearing defects [Van Camp, et al., *J. Med. Genet.* 36(7):532-6, (1999)], cherubism [Mangion, et al., *Am. J. Hum. Genet.* 65(1):151-7 (1999)], Wolf-Hirschhorn (WH) syndrome [Zollino, et al., *Am. J. Med. Genet.* 82(5):371-5 (1999); *Ann. Genet.* 41(2):73-6 (1998)], Ellis-van Creveld syndrome [EVC; Polymeropoulos, et al., *Genomics* 35(1):1-5 (1996)], autosomal dominant postaxial polydactyly, nail dystrophy, and dental abnormalities [Howard, et al., *Am. J. Hum. Genet.* 61(6):1405-12 (1997)], Pitt-Rogers-Danks (PRD) syndrome and overgrowth syndrome [Partington, et al., *J. Med. Genet.* 34(9):719-28 (1997)], bladder cancer and malignant brain

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tumors [Bell, et al., *Genes Chromosomes Cancer* 17(2):108-17 (1996)].

4) LP240

5 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:7 are contemplated by the present invention. Specifically, polypeptides of the present invention comprise the amino
10 acid sequence as shown in SEQ ID NO:8, as well as fragments, variants, and derivatives thereof. Accordingly, LP240 polynucleotides encoding LP240 polypeptides of the present invention are also contemplated by the present invention. The gene encoding the LP240 polypeptide as shown in SEQ ID
15 NO:8 has been localized to chromosome 19.

LP240 polynucleotides, polypeptides, and antibodies corresponding to LP240 are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, stroke, Alzheimer's disease,
20 Parkinson's disease, Huntington's disease, neurodegenerative disorders, brain cancer, cardiovascular disease, atherosclerosis, myocardial infarction, inflammation, and rheumatoid arthritis.

25 5) LP239(a) and LP239(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:9 and SEQ ID NO:23 are contemplated by the present invention.
30 Specifically, LP239(a) and LP239(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:10 and SEQ ID NO:24, respectively, as

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well as fragments, variants, and derivatives thereof. Accordingly, LP239(a) and LP239(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:9 and SEQ ID NO:23, respectively, are also contemplated by the
5 present invention.

LP239 polypeptide-encoding polynucleotide sequences are primarily expressed in digestive, hemic, immune, and nervous system tissues. The LP239(a) and LP239(b) polypeptides as shown in SEQ ID NO:10 and SEQ ID NO:24
10 share sequence similarity with a thyroxine-binding globulin [see AF204929; Mori, et al., *Endocr. J.* 46(4):613-9 (1999)]. LP239 polypeptides therefore may serve as hormone binding proteins in serum, protease inhibitors, or hormones when administered to patients suffering from a deficiency
15 of endogenous LP239 polypeptides. LP239 polynucleotides, polypeptides, and antibodies corresponding to LP239 are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, hypothyroidism, anemia, sepsis, gram negative
20 bacteremia, allergic responses, allergic autoimmune diseases, type 1 diabetes, Th1-dependent insulinitis, inflammation, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, liver failure, ARDS, cancers, leukemia, and immunodeficiency.

25

6) LP243(a) and LP243(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:11 and
30 SEQ ID NO:13 are contemplated by the present invention. Specifically, LP243(a) and LP243(b) polypeptides of the present invention comprise the amino acid sequences as shown

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in SEQ ID NO:12 and SEQ ID NO:14, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP243(a) and LP243(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:11 and SEQ ID
5 NO:13 are also contemplated by the present invention.

The gene encoding the disclosed LP243 polypeptides have been localized to chromosome 19p13.3 (GenBank hit g2894631) and is mainly expressed in nervous system and digestive system. The LP243 polypeptides as shown in SEQ ID NO:12 and
10 SEQ ID NO:14 share sequence similarity with the amino acid sequence of protein PRO227 disclosed in WO 99/14328, the amino acid sequence of the human Tango-79 protein disclosed in WO 99/06427, the glioma amplified on chromosome 1 (GAC1) protein (AF030435), and the *Rattus norvegicus* (AF133730)
15 SLIT protein. GAC1 is a member of the leucine-rich repeat superfamily on chromosome band 1q32.1. GAC1 is amplified and overexpressed in malignant gliomas [Almeida, et al., *Oncogene* 16(23):2997 (1998)]. In *Drosophila*, at least, SLIT proteins are believed to be involved in axon pathway
20 development. The two predicted proteins LP243(a) and LP243(b) as shown in SEQ ID NO:12 and 14, respectively, have different N-terminals but are identical starting from amino acid 27 through amino acid 557 as shown in SEQ ID NO:12. The present invention provides isolated LP243(a) and
25 LP243(b) polypeptides as described herein, wherein the polypeptide has at least one activity, such as, but not limited to, inducing cellular proliferation, tumorigenesis, synapse formation, neurotransmission, learning, cognition, homeostasis, neuronal outgrowth, differentiation or
30 survival, or tissue regeneration including but not limited to neural tissue regeneration. An LP243 polynucleotide,

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polypeptide, and/or antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP243 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP243 polynucleotides are expressed in nervous tissues and the polypeptides encoded thereby appear to play a role in tumorigenesis, neurodegenerative diseases, behavioral disorders, and/or inflammatory conditions. Accordingly, compositions comprising LP243 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, cancer, including, but not limited to sporadic ovarian tumors [Wang, et al., *Br. J. Cancer* 80(1-2):70-2 (1999)], Peutz-Jeghers syndrome [Nakagawa, et al., *Hum. Genet.* 102(2):203-6 (1998); Olschwang, et al., *J. Med. Genet.* 35(1):42-4 (1998)], adenoma malignum of the uterine cervix [Lee, et al., *Cancer Res.* 15;58(6):1140-3 (1998)], pancreatic carcinomas [Hoglund, et al., *Genes Chromosomes Cancer* 21(1):8-16 (1998)], multiple myeloma and plasma cell leukemia [Taniwaki, et al., *Blood* 84(7):2283-90 (1994)], Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and

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altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

7) LP253

5 Cytokines are secreted regulatory peptides that mediate a wide range of biological activities by binding to specific cell surface receptors on target cells. Cytokine actions include control of cell proliferation and differentiation, regulation of hematopoiesis, and immune inflammatory
10 responses. Cytokines are also major orchestrators of host defense processes and, as such, are involved in responses to exogenous as well as endogenous insults and in repair or restoration of tissue integrity. In order for a cytokine to exert its effect on cells, it is now accepted by those
15 skilled in the art that the molecule must interact with molecules, located on cell membranes, referred to as receptors. Patents which exemplify disclosures of interleukin receptors include Honjo, *et al.*, U.S. Patent 4,816,565; Urdal, *et al.*, U.S. Patent 4,578,335; Dower, *et al.*, U.S. Patent 5,180,812; and Taniguchi, *et al.*, U.S.
20 Patent 5,198,359; and WO 2000/15759, the disclosures of which are incorporated by reference.

In another embodiment of the present invention, we provide polypeptides comprising the amino acid sequence of
25 the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:15. Specifically, LP253 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:16, as well as fragments, variants, and derivatives thereof. Accordingly,
30 LP253 polynucleotides comprising polynucleotides as identified in SEQ ID NO:15 are also contemplated by the present invention. LP253 encoding polynucleotide sequences

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are primarily expressed in digestive, hemic, immune, and nervous system tissues. The LP253 polypeptide as shown in SEQ ID NO:16 shares structural similarity with other interleukin receptors.

5 The effects of IL-1 *in vivo* can be regulated via the administration of a soluble form of its receptor [Fanslow, et al., *Science* 248:739-41 (1990)]. Systemic administration of a soluble, extracellular portion of the receptor for IL-1 (soluble IL-1R) had profound inhibitory effects on the
10 development of *in vivo* alloreactivity. Survival of heterotopic heart allografts was prolonged from twelve days in controls to seventeen days in mice treated with soluble IL-1R. Lymph node hyperplasia in response to localized injection of allogeneic cells was completely blocked by
15 soluble IL-1R treatment.

 The availability of the purified LP253 polypeptide, in soluble form, presents therapeutic possibilities as well. The results that Fanslow report demonstrate the ability of a soluble cytokine receptor to modulate biological activity
20 upon exogenous administration *in vivo*, presumably by acting as a neutralizing agent for the endogeneously produced, corresponding ligand, and provides evidence of the therapeutic potential of soluble cytokine receptors in a variety of clinical disorders.

25 Administration of a soluble form of LP253 would interfere with the effect of its endogenous ligand on the cells, since the ligand would not bind to the endogenous membrane bound LP253 as freely. Hence, an aspect of the present invention is the treatment of pathological
30 conditions caused by excess expression and/or activity of LP253 polypeptides by adding an amount of soluble LP253 polypeptides sufficient to inhibit binding of a cytokine to

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the aforementioned cells. This methodology can also be modified, and the soluble receptor can also be used as a screening agent for pharmaceuticals. Briefly, a pharmaceutical which works as an LP253 antagonist can do so
5 by blocking the binding of endogenous ligand to the LP253. Prior to determining whether a material would be effective *in vivo*, one may use the purified LP253 polypeptide in connection with a potential pharmaceutical to determine if there is binding. If there is in fact binding, further
10 testing may be indicated.

Expression of recombinant polypeptides in high levels and its use as an antigen allows production of additional neutralizing monoclonal and polyclonal antibodies. Such neutralizing antibodies can be used in *in vivo* model
15 settings to elucidate the role that LP253 and its ligand play in normal as well as pathologic immune responses (i.e., disease states that are aggravated by activated T- and NK-cells like auto-immune diseases, graft versus host disease and rheumatoid arthritis). Thus, purified LP253
20 polypeptides, polynucleotides, and/or antibodies compositions will be useful in diagnostic assays for LP253 and its ligand, and also in raising antibodies to LP253 for use in diagnosis or therapy.

LP253 polypeptides, polynucleotides, and/or antibodies
25 can be administered, for example, for the purpose of suppressing immune responses in a human. A variety of diseases or conditions are caused by an immune response to alloantigen, including allograft rejection and graft-versus-host reaction. In alloantigen-induced immune responses,
30 soluble LP253 polypeptides may suppress lymphoproliferation and inflammation which result upon activation of T cells. Soluble LP253 polypeptides may therefore be used to

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effectively suppress alloantigen-induced immune responses in the clinical treatment of, for example, rejection of allografts (such as skin, kidney, and heart transplants), and graft-versus-host reactions in patients who have
5 received bone marrow transplants.

LP253 polypeptides, polynucleotides, and/or antibodies may also be used in clinical treatment of autoimmune dysfunctions, such a rheumatoid arthritis, diabetes and multiple sclerosis, which are dependent upon the activation
10 of T cells against antigens not recognized as being indigenous to the host. LP253 polypeptides, polynucleotides, and/or antibodies may also be useful in treatment of septic shock in which interferon gamma produced in response to various interleukins plays a central role in causing
15 morbidity and mortality [Doherty, et al., *J. Immunol.* 149:1666 (1992)]. In addition, compositions comprising soluble LP253 polypeptides may be used directly in therapy to bind or scavenge endogenous LP253 ligands, thereby providing a means for regulating the immune or inflammatory
20 activities. In its use to prevent or reverse pathologic immune responses, soluble LP253 polypeptides can be combined with other cytokine antagonists such as antibodies to the other known interleukin receptors, soluble interleukin receptors, soluble TNF (tumor necrosis factor) receptors,
25 and/or interleukin receptor antagonists, and the like.

The dose ranges for the administration of the LP253 polypeptides, polynucleotides, and/or antibodies and fragments thereof may be determined by those of ordinary skill in the art without undue experimentation. In general,
30 appropriate dosages are those which are large enough to produce the desired effect, for example, blocking the binding of endogenous ligands of LP253 to endogenous LP253.

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8) LP218

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:17 are contemplated by the present invention. Specifically, LP218 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:18, as well as fragments, variants, and derivatives thereof. Accordingly, LP218 polynucleotides comprising polynucleotides as identified in SEQ ID NO:17 are also contemplated by the present invention.

The gene encoding the LP218 polypeptide as shown in SEQ ID NO:18 has been localized to chromosome 22q11 and shares sequence similarity with acetyl LDL receptor. LP218 polynucleotides are expressed in hemic, immune, reproductive, and urinary tract tissues. Accordingly, compositions comprising LP218 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of schizophrenia [Li, *Mol. Psychiatry* 5(1):77-84 (2000)], hypocalcemia [Garabedian, et al., *Genet Couns.* 10(4):389-94 (1999)], rhabdoid tumor [Zhou, et al., *Gene* 241(1):133-41 (2000)], DiGeorge/velo-cardio-facial syndrome [Amati, et al., *Eur. J. Hum. Genet.* 7(8):903-9 (1999)], congenital heart disease [Borgmann, et al., *Eur. J. Pediatr.* 158(12):958-63 (1999)], and abdominal lymphatic dysplasia [Mansir, et al., *Genet. Couns.* 10(1):67-70 (1999)], oesophageal atresia [Digilio, et al., *J. Med. Genet.* 36(2):137-9 (1999)].

30

9) LP251(a) and LP251(b)

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In another embodiment, polypeptides comprising the amino acid sequence of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:19 and SEQ ID NO:33 are contemplated by the present invention.

5 Specifically, LP251(a) and LP251(b) polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:20 and SEQ ID NO:34, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP251(a) and LP251(b) polynucleotides comprising
10 polynucleotides as identified in SEQ ID NO:19 or SEQ ID NO:33 are also contemplated by the present invention.

The LP251 polypeptides as shown in SEQ ID NO:20 and SEQ ID NO:34 share sequence similarity with aqualysin I precursor, a subtilisin-type serine protease which is
15 secreted into the culture medium by *Thermus aquaticus* YT-1, an extremely thermophilic gram-negative bacterium [Terada, et al., *J. Biol. Chem.* 265(12):6576-81 (1990)].

The gene encoding the disclosed polypeptides has been localized to chromosome 1p33-p34.3. Accordingly,
20 compositions comprising LP251 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of breast cancer [Emi, et al., *Genes Chromosomes Cancer* 26(2):134-41 (1999)], myelodysplastic syndromes including but not limited to thrombocytopenia and
25 abnormal megakaryopoiesis [Jondeau, et al., *Leukemia* 10(11):1692-5 (1996)], Schnyder's crystalline corneal dystrophy [Shearman, et al., *Hum. Mol. Genet.* 5(10):1667-72 (1996)], tumorigenesis including, but not limited to, colorectal cancer [Praml, et al., *Oncogene* 11(7):1357-62 (1995)], Schwartz-Jampel syndrome [Nicole, *Hum. Mol. Genet.* 4(9):1633-6 (1995)], and autosomal dominant hypercholesterol-

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emia [Varret, et al., *Am. J. Hum. Genet.* 64(5):1378-87 (1999)].

Furthermore, LP251 polynucleotides are mainly expressed in skin and liver. Accordingly, compositions comprising
5 LP251 polypeptides, polynucleotides, and/or antibodies are generally useful for the treatment of defects in or wounds to tissues including, but not limited to skin and liver.

10) LP252

10 In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:21 are contemplated by the present invention. Specifically, LP252 polypeptides of the present invention comprise the amino
15 acid sequence as shown in SEQ ID NO:22, as well as fragments, variants, and derivatives thereof. Accordingly, LP252 polynucleotides comprising polynucleotides as identified in SEQ ID NO:21 are also contemplated by the present invention.

20 The LP252 polypeptide as shown in SEQ ID NO:22 shares sequence similarity with thyroid hormone-induced protein B precursor. Furthermore, the gene encoding the disclosed polypeptide has been localized to chromosome 9p12-13. Accordingly, compositions comprising LP252 polypeptides,
25 polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of ectrodactyly, ectodermal dysplasia and cleft lip/palate syndrome [Fukushima, et al., *Clin. Genet.* 44(1):50 (1993); Hasegawa, et al., *Clin. Genet.* 40(3):202-6 (1991)]; and cancer, including, but not limited
30 to, kidney cancer and carcinoma of the respiratory tract [Schraml, et al., *J. Pathol.* 190(4):457-61 (2000); Higashi, et al., *Genes Chromosomes Cancer* 3(1):21-3 (1991)].

11) LP223(a) and (b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:25 and SEQ ID NO:37 are contemplated by the present invention. Specifically, LP223(a) and LP223(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:26 and SEQ ID NO:38, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP223(a) and LP223(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:25 and SEQ ID NO:37 are also contemplated by the present invention. The LP223(a) and LP223(b) polypeptides as shown in SEQ ID NO:26 and SEQ ID NO:38 share sequence similarity with a human secreted protein sequence disclosed in WO 2000/04140.

The present invention also provides isolated LP223 polypeptides as described herein, wherein the polypeptides have at least one activity, such as, but not limited to, inducing cellular proliferation, synapse formation, neurotransmission, learning, cognition, homeostasis, neuronal outgrowth, differentiation or survival, or tissue regeneration including but not limited to neural tissue regeneration. An LP223 polynucleotide, polypeptide, and/or antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP223 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP223 polynucleotides and polypeptides are expressed in

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nervous tissues and appear to play a role in neurodegenerative diseases, behavioral disorders, and/or inflammatory conditions. Accordingly, compositions comprising LP223 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system.

12) LP255(a) and LP255(b)

In another embodiment, polypeptides comprising the amino acid sequences of the open reading frames encoded by the polynucleotide sequences as shown in SEQ ID NO:27 and SEQ ID NO:35 are contemplated by the present invention. Specifically, LP255(a) and LP255(b) polypeptides of the present invention comprise the amino acid sequences as shown in SEQ ID NO:28 and SEQ ID NO:36, respectively, as well as fragments, variants, and derivatives thereof. Accordingly, LP255(a) and LP255(b) polynucleotides comprising polynucleotides as identified in SEQ ID NO:27 and SEQ ID

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NO:35 are also contemplated by the present invention. The LP255(a) and LP255(b) polypeptides as shown in SEQ ID NO:28 and SEQ ID NO:36 share sequence similarity with a human secreted protein sequence disclosed in WO 99/14328 as
5 PRO332.

The present invention also provides isolated LP255 polypeptides as described herein, wherein the polypeptides have at least one activity, such as, but not limited to, promoting cell growth. An LP255 polynucleotide,
10 polypeptide, and/or antibody can thus be screened for a corresponding activity according to known methods.

The present invention also provides a composition comprising an isolated LP255 nucleic acid, polypeptide, and/or antibody as described herein and a carrier or
15 diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known methods. LP255 polynucleotides and polypeptides are expressed in nervous tissues and appear to play a role in neurological disorders. Accordingly, compositions comprising LP255
20 polypeptides, polynucleotides, and/or antibodies are useful for diagnosis, treatment and intervention of diseases, disorders, and/or conditions arising from Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases,
25 peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic
disorder learning disabilities, ALS, psychoses, autism, and
30 altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

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13) LP244

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:29 are
5 contemplated by the present invention. Specifically, LP244 polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:30, as well as fragments, variants, and derivatives thereof. Accordingly, LP244 polynucleotides comprising polynucleotides as
10 identified in SEQ ID NO:29 are also contemplated by the present invention.

The gene encoding the LP244 polypeptide has been localized to chromosome 19 and is predominantly expressed in embryonic structures. The LP244 polypeptide as shown in SEQ
15 ID NO:30 appears to be a novel shortened splice-variant of the human Epstein-Barr virus induced gene 3 (EBI3; GenBank accession no. NP_005746) wherein the first 67 amino acids of the LP244 polypeptide are identical to those of EBI3. EBI3 is reported to be a hematopoietin receptor family
20 member related to the p40 subunit of interleukin-12 and to the ciliary neurotrophic factor receptor, whose expression is induced in B lymphocytes by Epstein-Barr virus (EBV) infection [Devergne, et al., *J. Virology* 70(2):1143-53 (1996)]. The gene encodes a 34-kDa glycoprotein which lacks
25 a membrane-anchoring motif and is secreted. Despite the absence of a membrane-anchoring motif and of cysteines likely to mediate covalent linkage to an integral membrane protein, EBI3 is also present on the plasma membrane of EBV-transformed B lymphocytes and of transfected cells. Most
30 newly synthesized EBI3 is retained in the endoplasmic reticulum in an endoglycosidase H-sensitive form associated with the molecular chaperone calnexin and with a novel 60-

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kDa protein. EBI3 is expressed *in vivo* by scattered cells in interfollicular zones of tonsil tissue, by cells associated with sinusoids in perifollicular areas of spleen tissue, and at very high levels by placental syncytio-

5 trophoblasts. EBI3 expression *in vitro* is induced in EBV-negative cell lines by expression of the EBV latent infection membrane protein-1 and in peripheral blood mononuclear cells by pokeweed mitogen stimulation. EBI3 maps to chromosome 19p13.2/3, near genes encoding the

10 erythropoietin receptor and the cytokine receptor-associated kinase, Tyk2. EBI3 synthesis by trophoblasts and by EBV-transformed cells and similarities to interleukin-12 p40 are compatible with a role for EBI3 in regulating cell-mediated immune responses. LP244 therefore may function as a

15 modulator of EBI3 activity. Administration of a soluble form of LP244 would interfere with the effect of its endogenous ligand on the cells, since the ligand would not bind to the endogenous membrane bound LP244 as freely. Hence, an aspect of the present invention is the treatment

20 of pathological conditions caused by excessive expression of LP244 polypeptides by adding an amount of soluble LP244 polypeptides sufficient to inhibit binding of a cytokine to the aforementioned cells. This methodology can also be modified, and the soluble receptor can also be used as a

25 screening agent for pharmaceuticals. Briefly, a pharmaceutical which works as an LP244 antagonist can do so by blocking the binding of endogenous ligand to the LP244. Prior to determining whether a material would be effective *in vivo*, one may use the purified LP244 polypeptide in

30 connection with a potential pharmaceutical to determine if there is binding. If there is in fact binding, further testing may be indicated.

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Expression of recombinant polypeptides in high levels and its use as an antigen allows production of additional neutralizing monoclonal and polyclonal antibodies. Such neutralizing antibodies can be used in *in vivo* model

5 settings to elucidate the role that LP244 and its ligand play in normal as well as pathologic immune responses (i.e., disease states that are aggravated by activated T- and NK-cells like autoimmune diseases, graft versus host disease, and rheumatoid arthritis). Thus, purified LP244 polypep-
10 tides, polynucleotides, and/or antibodies compositions will be useful in diagnostic assays for LP244 and its ligand, and also in raising antibodies to LP244 for use in diagnosis or therapy. More specifically, compositions comprising LP244 polypeptides, polynucleotides, and/or antibodies are useful
15 for diagnosis, treatment and intervention of diseases, disorders, and/or conditions including, but not limited to, infectious diseases, hypothyroidism, anemia, sepsis, gram negative bacteremia, allergic responses, allergic autoimmune diseases, type 1 diabetes, Th1-dependent insulinitis,
20 inflammation, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, liver failure, ARDS, cancers, leukemia, and immuno-deficiency, arthritis, leukemia, lymphomas, immuno-suppression, immunity, humoral immunity, myelosuppression, periodontal disease, and osteoarthritis.

25 LP244 polypeptides, polynucleotides, and/or antibodies can be administered, for example, for the purpose of suppressing immune responses in a human. A variety of diseases or conditions are caused by an immune response to alloantigen, including allograft rejection and graft-versus-
30 host reaction. In alloantigen-induced immune responses, soluble LP244 polypeptides may suppress lymphoproliferation and inflammation which result upon activation of T cells.

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Soluble LP244 polypeptides may therefore be used to effectively suppress alloantigen-induced immune responses in the clinical treatment of, for example, rejection of allografts (such as skin, kidney, and heart transplants), and graft-versus-host reactions in patients who have received bone marrow transplants.

LP244 polypeptides, polynucleotides, and/or antibodies may also be used in clinical treatment of autoimmune dysfunctions, such as rheumatoid arthritis, diabetes and multiple sclerosis, which are dependent upon the activation of T cells against antigens not recognized as being indigenous to the host. LP244 polypeptides, polynucleotides, and/or antibodies may also be useful in treatment of septic shock in which interferon gamma produced in response to various interleukins plays a central role in causing morbidity and mortality [Doherty, et al., *J. Immunol.* 149:1666 (1992)]. In addition, compositions comprising soluble LP244 compositions may be used directly in therapy to bind or scavenge endogenous LP244 ligands, thereby providing a means for regulating the immune or inflammatory activities. In its use to prevent or reverse pathologic immune responses, soluble LP244 polypeptides can be combined with other cytokine antagonists such as antibodies to the other known interleukin receptors, soluble interleukin receptors, soluble TNF (tumor necrosis factor) receptors, and/or interleukin receptor antagonists, and the like.

14) LP186

In another embodiment, polypeptides comprising the amino acid sequence of the open reading frame encoded by the polynucleotide sequence as shown in SEQ ID NO:31 are contemplated by the present invention. Specifically, LP186

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polypeptides of the present invention comprise the amino acid sequence as shown in SEQ ID NO:32, as well as fragments, variants, and derivatives thereof. Accordingly, LP186 polynucleotides comprising polynucleotides as
5 identified in SEQ ID NO:31 are also contemplated by the present invention.

The LP186 polypeptide as shown in SEQ ID NO:32 shares sequence similarity with the human delta homologue, DLL3 [Bulman, et al., *Nature Genetics* 24(4):438-41 (2000)].
10 Mutations in the human delta homologue, DLL3, cause axial skeletal defects in spondylocostal dysostosis. Two of the mutations predict truncations within conserved extracellular domains. The third is a missense mutation in a highly conserved glycine residue of the fifth epidermal growth
15 factor (EGF) repeat, which has revealed an important functional role for this domain. Spondylocostal dysostosis (SD) is a group of vertebral malsegmentation syndromes with reduced stature resulting from axial skeletal defects. SD is characterized by multiple hemivertebrae, rib fusions and
20 deletions with a non-progressive kyphoscoliosis. Dll3 is mutated in the X-ray-induced mouse mutant pudgy (pu), causing a variety of vertebrocostal defects similar to SD phenotypes [Kusumi, et al., *Nature Genetics* 19(3):274-8 (1998)]. These mutations highlight the critical role of the
25 Notch signalling pathway and its components in patterning the mammalian axial.

LP186 polypeptide-encoding polynucleotide sequences are primarily expressed in the nervous system. Thus, polynucleotides, polypeptides, and antibodies corresponding
30 to this gene are useful for diagnosis, treatment and intervention of diseases, disorders, and conditions of the nervous system. Thus, the present sequence represents a

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polypeptide which suppresses proliferation and differentiation of undifferentiated cells such as neurons and blood cells. The polypeptide may be used for the prevention and control of disorders involving undifferentiated cells, such as leukaemia and malignant tumours, and improvement of blood formation, e.g., after immunosuppression.

The polynucleotides and polypeptides of the present invention are designated herein as "LP polynucleotides" or "LP polypeptide-encoding polynucleotides" and "LP polypeptides." When immediately followed by a numerical designation (i.e., LP105), the term "LP" refers to a specific group of molecules as defined herein. A complete designation wherein the term "LP" is immediately followed by a numerical designation and a molecule type (i.e., LP105 polypeptide) refers to a specific type of molecule within the designated group of molecules as designated herein.

The terms "LP polypeptide-encoding polynucleotides" or "LP polynucleotides" and "LP polypeptides" wherein the term "LP" is followed by an actual numerical designation as used herein encompass novel polynucleotides and polypeptides, respectively, which are further defined herein. The LP molecules described herein may be isolated from a variety of sources including, but not limited to human tissue types, or prepared by recombinant or synthetic methods.

One aspect of the present invention provides an isolated nucleic acid molecule comprising a polynucleotide which encodes an LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide as defined herein. In a preferred embodiment of the present invention, the isolated

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nucleic acid comprises 1) a polynucleotide encoding an LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide having an amino acid sequence as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38, respectively; 2) a polynucleotide complementary to such encoding nucleic acid sequences, and which remain stably bound to them under at least moderate, and optionally, high stringency conditions; or 3) any fragment and/or variant of 1) or 2).

The term "LP polypeptide" specifically encompasses truncated or secreted forms of an LP polypeptide, (e.g., soluble forms containing, for instance, an extracellular domain sequence), variant forms (e.g., alternatively spliced forms) and allelic variants of an LP polypeptide.

In one embodiment of the invention, the native sequence LP polypeptide is a full-length or mature LP polypeptide comprising amino acids as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38. The predicted signal peptides are indicated in the sequence listing of the present application by negative integers below the amino acids disclosed for a particular polypeptide. Also, while the LP polypeptides disclosed herein are shown to begin with a methionine residue designated as amino acid position 1, it is conceivable and possible that another methionine residue located either upstream or downstream from amino acid position 1 may be employed as the starting amino acid residue.

A "portion" of an LP polypeptide sequence is at least about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80,

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85, 90, 95, or 100 contiguous amino acid residues in length.

"LP polypeptide variant" is intended to refer to an "active" LP polypeptide, wherein activity is as defined
5 herein, having at least about 90% amino acid sequence identity with an LP polypeptide having a deduced amino acid sequences as shown above. Such LP polypeptide variants include, for instance, LP polypeptides, wherein one or more amino acid residues are added, substituted or deleted, at
10 the N- or C-terminus or within the sequences shown. Ordinarily, an LP polypeptide variant will have at least about 90% amino acid sequence identity, preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least
15 about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least
20 about 98% sequence identity, yet more preferably at least about 99% amino acid sequence identity with the amino acid sequence described, with or without the signal peptide.

"Percent (%) amino acid sequence identity" with respect to the LP amino acid sequences identified herein is
25 defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in an LP polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering
30 any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various

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ways that are within the skill in the art, for instance, using publicly available computer software such as ALIGN, ALIGN-2, Megalign (DNASTAR) or BLAST (e.g., Blast, Blast-2, WU-Blast-2) software. Those skilled in the art can

5 determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, the percent identity values used herein are generated using WU-BLAST-2 [Altschul, et al.,

10 *Methods in Enzymology* 266:460-80 (1996)]. Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1; overlap fraction = 0.125; word threshold

15 (T) = 11; and scoring matrix = BLOSUM 62. For purposes herein, a percent amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the LP polypeptide of interest and the comparison amino acid

20 sequence of interest (i.e., the sequence against which the LP polypeptide of interest is being compared) as determined by WU-BLAST-2, by (b) the total number of amino acid residues of the LP polypeptide of interest, respectively.

An "LP variant polynucleotide," "LP polynucleotide

25 variant," or "LP variant nucleic acid sequence" are intended to refer to a nucleic acid molecule as defined below having at least about 75% nucleic acid sequence identity with the polynucleotide sequence as shown in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27,

30 29, 31, 33, 35, or 37. Ordinarily, an LP polynucleotide variant will have at least about 75% nucleic acid sequence identity, more preferably at least about 80% nucleic acid

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sequence identity, yet more preferably at least about 81% nucleic acid sequence identity, yet more preferably at least about 82% nucleic acid sequence identity, yet more preferably at least about 83% nucleic acid sequence identity, yet more preferably at least about 84% nucleic acid sequence identity, yet more preferably at least about 85% nucleic acid sequence identity, yet more preferably at least about 86% nucleic acid sequence identity, yet more preferably at least about 87% nucleic acid sequence identity, yet more preferably at least about 88% nucleic acid sequence identity, yet more preferably at least about 89% nucleic acid sequence identity, yet more preferably at least about 90% nucleic acid sequence identity, yet more preferably at least about 91% nucleic acid sequence identity, yet more preferably at least about 92% nucleic acid sequence identity, yet more preferably at least about 93% nucleic acid sequence identity, yet more preferably at least about 94% nucleic acid sequence identity, yet more preferably at least about 95% nucleic acid sequence identity, yet more preferably at least about 96% nucleic acid sequence identity, yet more preferably at least about 97% nucleic acid sequence identity, yet more preferably at least about 98% nucleic acid sequence identity, yet more preferably at least about 99% nucleic acid sequence identity with the nucleic acid sequences shown above. Variants specifically exclude or do not encompass the native nucleotide sequence, as well as those prior art sequences that share 100% identity with the nucleotide sequences of the invention.

30 "Percent (%) nucleic acid sequence identity" with respect to the LP polynucleotide sequences identified herein is defined as the percentage of nucleotides in a

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candidate sequence that are identical with the nucleotides in the LP polynucleotide sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as ALIGN, Align-2, Megalign (DNASTAR), or BLAST (e.g., Blast, Blast-2) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % nucleic acid identity values are generated using the WU-BLAST-2 (BlastN module) program [Altschul, et al., *Methods in Enzymology* 266:460-80 (1996)]. Most of the WU-BLAST-2 search parameters are set to the default values. Those not set default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1; overlap fraction = 0.125; word threshold (T) = 11; and scoring matrix = BLOSUM62. For purposes herein, a percent nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the LP polypeptide-encoding nucleic acid molecule of interest and the comparison nucleic acid molecule of interest (i.e., the sequence against which the LP polypeptide-encoding nucleic acid molecule of interest is being compared) as determined by WU-BLAST-2, by (b) the total number of nucleotides of the LP polypeptide-encoding nucleic acid molecule of interest.

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In other embodiments, the LP variant polypeptides are encoded by nucleic acid molecules which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length LP polypeptide as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38. This scope of variant polynucleotides specifically excludes those sequences that are known as of the filing and/or priority dates of the present application.

10 The term "mature protein" or "mature polypeptide" as used herein refers to the form(s) of the protein produced by expression in a mammalian cell. It is generally hypothesized that once export of a growing protein chain across the rough endoplasmic reticulum has been initiated, proteins secreted by mammalian cells have a signal peptide (SP) sequence which is cleaved from the complete polypeptide to produce a "mature" form of the protein. Oftentimes, cleavage of a secreted protein is not uniform and may result in more than one species of mature protein.

20 The cleavage site of a secreted protein is determined by the primary amino acid sequence of the complete protein and generally cannot be predicted with complete accuracy. Methods for predicting whether a protein has an SP sequence, as well as the cleavage point for that sequence, are available. A cleavage point may exist within the N-terminal domain between amino acid 10 and amino acid 35. More specifically the cleavage point is likely to exist after amino acid 15 but before amino acid 30, more likely after amino acid 27. As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Optimally, cleavage sites for a secreted

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protein are determined experimentally by amino-terminal sequencing of the one or more species of mature proteins found within a purified preparation of the protein.

The term "positives," in the context of sequence comparison performed as described above, includes residues in the sequences compared that are not identical but have similar properties (e.g., as a result of conservative substitutions). The percent identity value of positives is determined by the fraction of residues scoring a positive value in the BLOSUM 62 matrix. This value is determined by dividing (a) the number of amino acid residues scoring a positive value in the BLOSUM62 matrix of WU-BLAST-2 between the LP polypeptide amino acid sequence of interest and the comparison amino acid sequence (i.e., the amino acid sequence against which the LP polypeptide sequence is being compared) as determined by WU-BLAST-2, by (b) the total number of amino acid residues of the LP polypeptide of interest.

"Isolated," when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2)

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to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the LP polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated LP polypeptide-encoding nucleic acid" or "isolated LP nucleic acid" is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the nucleic acid. Such an isolated nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the nucleic acid molecule as it exists in natural cells. However, an isolated LP polypeptide-encoding nucleic acid molecule includes LP polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express LP polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably

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linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation
5 at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

The term "amino acid" is used herein in its broadest sense, and includes naturally occurring amino acids as well
10 as non-naturally occurring amino acids, including amino acid analogs and derivatives. The latter includes molecules containing an amino acid moiety. One skilled in the art will recognize, in view of this broad definition, that reference herein to an amino acid includes, for
15 example, naturally occurring proteogenic L-amino acids; D-amino acids; chemically modified amino acids such as amino acid analogs and derivatives; naturally-occurring non-proteogenic amino acids such as norleucine, beta-alanine, ornithine, etc.; and chemically synthesized compounds
20 having properties known in the art to be characteristic of amino acids. As used herein, the term "proteogenic" indicates that the amino acid can be incorporated into a peptide, polypeptide, or protein in a cell through a metabolic pathway.

25 The incorporation of non-natural amino acids, including synthetic non-native amino acids, substituted amino acids, or one or more D-amino acids into the LP peptides, polypeptides, or proteins of the present invention ("D-LP polypeptides") is advantageous in a number
30 of different ways. D-amino acid-containing peptides, polypeptides, or proteins exhibit increased stability *in vitro* or *in vivo* compared to L-amino acid-containing

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counterparts. Thus, the construction of peptides, polypeptides, or proteins incorporating D-amino acids can be particularly useful when greater intracellular stability is desired or required. More specifically, D-peptides, polypeptides, or proteins are resistant to endogenous peptidases and proteases, thereby providing improved bioavailability of the molecule and prolonged lifetimes in vivo when such properties are desirable. When it is desirable to allow the peptide, polypeptide, or protein to remain active for only a short period of time, the use of L-amino acids therein will permit endogenous peptidases, proteases, etc., in a cell to digest the molecule in vivo, thereby limiting the cell's exposure to the molecule. Additionally, D-peptides, polypeptides, or proteins cannot be processed efficiently for major histocompatibility complex class II-restricted presentation to T helper cells, and are therefore less likely to induce humoral immune responses in the whole organism.

In addition to using D-amino acids, those of ordinary skill in the art are aware that modifications in the amino acid sequence of a peptide, polypeptide, or protein can result in equivalent, or possibly improved, second generation peptides, polypeptides, or proteins, that display equivalent or superior functional characteristics when compared to the original amino acid sequences. Alterations in the LP peptides, polypeptides, or proteins of the present invention can include one or more amino acid insertions, deletions, substitutions, truncations, fusions, shuffling of subunit sequences, and the like, either from natural mutations or human manipulation, provided that the sequences produced by such modifications have substantially the same (or improved or reduced, as may be desirable)

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activity(ies) as the naturally-occurring counterpart sequences disclosed herein.

One factor that can be considered in making such changes is the hydropathic index of amino acids. The importance of the hydropathic amino acid index in conferring interactive biological function on a protein has been discussed by Kyte and Doolittle [*J. Mol. Biol.* 157:105-32 (1982)]. It is accepted that the relative hydropathic character of amino acids contributes to the secondary structure of the resultant protein. This, in turn, affects the interaction of the protein with molecules such as enzymes, substrates, receptors, ligands, DNA, antibodies, antigens, etc. Based on its hydrophobicity and charge characteristics, each amino acid has been assigned a hydropathic index as follows: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate/glutamine/aspartate/asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

As is known in the art, certain amino acids in a peptide, polypeptide, or protein can be substituted for other amino acids having a similar hydropathic index or score and produce a resultant peptide, polypeptide, or protein having similar biological activity, i.e., which still retains biological functionality. In making such changes, it is preferable that amino acids having hydropathic indices within ± 2 are substituted for one another. More preferred substitutions are those wherein the amino acids have hydropathic indices within ± 1 . Most

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preferred substitutions are those wherein the amino acids have hydropathic indices within ± 0.5 .

Like amino acids can also be substituted on the basis of hydrophilicity. U.S. Patent 4,554,101 discloses that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein. The following hydrophilicity values have been assigned to amino acids: arginine/lysine (+3.0); aspartate/glutamate (+3.0 \pm 1); serine (+0.3); asparagine/glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 \pm 1); alanine/histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine/isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); and tryptophan (-3.4). Thus, one amino acid in a peptide, polypeptide, or protein can be substituted by another amino acid having a similar hydrophilicity score and still produce a resultant peptide, polypeptide, or protein having similar biological activity, i.e., still retaining correct biological function. In making such changes, amino acids having hydropathic indices within ± 2 are preferably substituted for one another, those within ± 1 are more preferred, and those within ± 0.5 are most preferred.

As outlined above, amino acid substitutions in the LP polypeptides of the present invention can be based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, etc. Exemplary substitutions that take various of the foregoing characteristics into consideration in order to produce conservative amino acid changes resulting in silent changes within the present

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peptides, polypeptides, or proteins can be selected from other members of the class to which the naturally occurring amino acid belongs. Amino acids can be divided into the following four groups: (1) acidic amino acids; (2) basic amino acids; (3) neutral polar amino acids; and (4) neutral non-polar amino acids. Representative amino acids within these various groups include, but are not limited to: (1) acidic (negatively charged) amino acids such as aspartic acid and glutamic acid; (2) basic (positively charged) amino acids such as arginine, histidine, and lysine; (3) neutral polar amino acids such as glycine, serine, threonine, cysteine, cystine, tyrosine, asparagine, and glutamine; and (4) neutral non-polar amino acids such as alanine, leucine, isoleucine, valine, proline, phenyl-alanine, tryptophan, and methionine.

It should be noted that changes which are not expected to be advantageous can also be useful if these result in the production of functional sequences. Since small peptides polypeptides, and some proteins can be easily produced by conventional solid phase synthetic techniques, the present invention includes peptides, polypeptides, or proteins such as those discussed herein, containing the amino acid modifications discussed above, alone or in various combinations. To the extent that such modifications can be made while substantially retaining the activity of the peptide, polypeptide, or protein, they are included within the scope of the present invention. The utility of such modified peptides, polypeptides, or proteins can be determined without undue experimentation by, for example, the methods described herein.

While biologically functional equivalents of the present LP polypeptides can have any number of conservative

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or non-conservative amino acid changes that do not significantly affect their activity(ies), or that increase or decrease activity as desired, 40, 30, 20, 10, 5, or 3 changes, such as 1 to 30 changes or any range or value
5 therein, may be preferred. In particular, ten or fewer amino acid changes may be preferred. More preferably, seven or fewer amino acid changes may be preferred; most preferably, five or fewer amino acid changes may be preferred. The encoding nucleotide sequences (gene, plasmid
10 DNA, cDNA, synthetic DNA, or mRNA, for example) will thus have corresponding base substitutions, permitting them to code on expression for the biologically functional equivalent forms of the LP polypeptides. In any case, the LP peptides, polypeptides, or proteins exhibit the same or
15 similar biological or immunological activity(ies) as that(those) of the LP polypeptides specifically disclosed herein, or increased or reduced activity, if desired. The activity(ies) of the variant LP polypeptides can be determined by the methods described herein. Variant LP
20 polypeptides biologically functionally equivalent to those specifically disclosed herein have activity(ies) differing from those of the presently disclosed molecules by about $\pm 50\%$ or less, preferably by about $\pm 40\%$ or less, more preferably by about $\pm 30\%$ or less, more preferably by about
25 $\pm 20\%$ or less, and even more preferably by about $\pm 10\%$ or less, when assayed by the methods disclosed herein.

Amino acids in an LP polypeptide of the present invention that are essential for activity can be identified by methods known in the art, such as site-directed
30 mutagenesis or alanine-scanning mutagenesis [Cunningham and Wells, *Science* 244:1081-5 (1989)]. The latter procedure introduces single alanine mutations at every residue in the

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molecule. The resulting mutant molecules are then tested for biological activity. Sites that are critical for ligand-protein binding can also be identified by structural analysis such as crystallization, nuclear magnetic
5 resonance, or photoaffinity labeling [Smith, et al., *J. Mol. Biol.* 224:899-904 (1992); de Vos, et al., *Science* 255:306-12 (1992)].

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and
10 generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer nucleic acid probes required higher temperatures for proper annealing, while shorter nucleic acid probes need lower temperatures. Hybridization
15 generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature
20 that can be used. As a result, it follows that higher relative temperatures would tend to make the reactions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel, et al., *Current Protocols in*
25 *Molecular Biology*, Wiley Interscience Publishers (1995).

"Stringent conditions" or "high stringency conditions," as defined herein, may be identified by those that (1) employ low ionic strength and high temperature for washing, for example, 15 mM sodium chloride/1.5 mM sodium
30 citrate/0.1% sodium dodecyl sulfate at 50 degrees C;
(2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1%

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bovine serum albumin/0.1% ficoll/0.1% polyvinylpyrrol-
idone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM
sodium chloride/75 mM sodium citrate at 42 degrees C; or
(3) employ 50% formamide, 5X SSC (750 mM sodium chloride,
5 75 mM sodium citrate), 50 mM sodium phosphate (pH 6.8),
0.1% sodium pyrophosphate, 5X Denhardt's solution,
sonicated salmon sperm DNA (50 µg/mL), 0.1% SDS, and 10%
dextran sulfate at 42 degrees C with washes at 42 degrees C
in 0.2X SSC (30 mM sodium chloride/3 mM sodium citrate) and
10 50% formamide at 55 degrees C, followed by a high-
stringency wash consisting of 0.1X SSC containing EDTA at
55 degrees C.

"Moderately stringent conditions" may be identified as
described by Sambrook, et al. [*Molecular Cloning: A*
15 *Laboratory Manual*, New York: Cold Spring Harbor Press,
(1989)], and include the use of washing solution and
hybridization conditions (e.g., temperature, ionic strength
and %SDS) less stringent than those described above. An
example of moderately stringent conditions is overnight
20 incubation at 37 degrees C in a solution comprising: 20%
formamide, 5X SSC (750 mM sodium chloride, 75 mM sodium
citrate), 50 mM sodium phosphate at pH 7.6, 5X Denhardt's
solution, 10% dextran sulfate, and 20 mg/mL denatured
sheared salmon sperm DNA, followed by washing the filters
25 in 1X SSC at about 37 to 50 degrees C. The skilled artisan
will recognize how to adjust the temperature, ionic
strength, etc., as necessary to accommodate factors such as
probe length and the like.

The term "epitope tagged" where used herein refers to
30 a chimeric polypeptide comprising an LP polypeptide, or
domain sequence thereof, fused to a "tag polypeptide." The
tag polypeptide has enough residues to provide an epitope

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against which an antibody may be made, or which can be identified by some other agent, yet is short enough such that it does not interfere with the activity of the LP polypeptide. The tag polypeptide preferably is also fairly
5 unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about eight to about fifty amino acid residues (preferably, between about ten to about twenty residues).

10 As used herein, the term "immunoadhesin," sometimes referred to as an Fc fusion, designates antibody-like molecules that combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains.
15 Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part
20 of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3 or IgG-4
25 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of LP polypeptide which retain all or a portion of the biologic and/or immunologic activities of native or naturally-occurring LP polypeptide. Elaborating further,
30 "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring LP polypeptide other than the ability

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to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring LP polypeptide. An "immunological" activity refers only to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring LP polypeptide.

The term "antagonist" is used in the broadest sense and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native LP polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native LP polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native LP polypeptides, peptides, ribozymes, anti-sense nucleic acids, small organic molecules, etc. Methods for identifying agonists or antagonists of an LP polypeptide may comprise contacting an LP polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the LP polypeptide.

"Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact

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monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

5 The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventive therapy. An example of "preventive therapy" is the prevention or lessened targeted pathological condition or disorder. Those in need of
10 treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

 "Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute
15 mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption but, rather, is cyclic in nature.

 Administration "in combination with" one or more
20 further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

 A "therapeutically-effective amount" is the minimal amount of active agent (e.g., an LP polypeptide, antagonist or agonist thereof) which is necessary to impart therapeutic
25 benefit to a mammal. For example, a "therapeutically-effective amount" to a mammal suffering or prone to suffering or to prevent it from suffering is such an amount which induces, ameliorates, or otherwise causes an improvement in the pathological symptoms, disease
30 progression, physiological conditions associated with or resistance to succumbing to the aforescribed disorder.

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"Carriers" as used herein include pharmaceutically-acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the

5 physiologically-acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecule weight (less than about 10 residues)

10 polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose,

15 mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN[®], polyethylene glycol (PEG), and PLURONIC[®].

"Antibody fragments" comprise a portion of an intact

20 antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments; diabodies; linear antibodies [Zapata, et al., *Protein Engin.* 8 (10):1057-62 (1995)]; single-chain antibody molecules; and

25 multispecific antibodies formed from antibody fragments.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is

30 in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_HV_L dimer. Collectively, the six CDRs

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confer antigen-binding specificity to the antibody.

However, even a single variable domain (or half of an Fv comprising only three CDR specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domain, which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun, *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore, eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H - V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404 097; WO 93/11161; and Hollinger, et al., *Proc. Natl. Acad. Sci. USA* 90:6444-8 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the

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antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or
5 internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue, or preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least
10 one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An "LP polypeptide antibody" or "LP antibody" refers to an antibody as defined herein that recognizes and binds
15 at least one epitope of an LP polypeptide of the present invention. The term "LP polypeptide antibody" or "LP antibody" wherein the term "LP" is followed by a numerical designation refers to an antibody that recognizes and binds to at least one epitope of that particular LP polypeptide
20 as disclosed herein.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as an LP polypeptide or antibody thereto) to a mammal. The components of the
25 liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 daltons.

The term "modulate" means to affect (e.g., either
30 upregulate, downregulate or otherwise control) the level of a signaling pathway. Cellular processes under the control of signal transduction include, but are not limited to,

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transcription of specific genes, normal cellular functions, such as metabolism, proliferation, differentiation, adhesion, apoptosis and survival, as well as abnormal processes, such as transformation, blocking of
5 differentiation and metastasis.

An LP polynucleotide can be composed of any polyribo-nucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, the LP polynucleotides can be composed of single- and
10 double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a
15 mixture of single- and double-stranded regions. In addition, LP polynucleotides can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. LP polynucleotides may also contain one or more modified bases or DNA or RNA backbones modified for stability or for
20 other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

25 LP polypeptides can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the gene-encoded amino acids. The LP polypeptides may be modified by either natural processes, such as post-
30 translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more

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detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in the LP polypeptides, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given LP polypeptide. Also, a given LP polypeptide may contain many types of modifications. LP polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic LP polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, Creighton, *Proteins - Structure and Molecular Properties*, 2nd Ed., W. H. Freeman and Company, New York (1993); Johnson, *Post-translational Covalent Modification of Proteins*, Academic Press, New York, pp. 1-12 (1983);

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Seifter, et al., *Meth. Enzymol.* 182:626-46 (1990); Rattan, et al., *Ann. NY Acad. Sci.* 663:48-62 (1992).

Variations in the full-length sequence LP polypeptide or in various domains of the LP polypeptide described
5 herein can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding LP
10 polypeptide that results in a change in the amino acid sequence of the LP polypeptide as compared with the native sequence LP polypeptide or an LP polypeptide as disclosed herein. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or
15 more of the domains of the LP polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the LP polypeptide with that of homologous known protein
20 molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine
25 with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of one to five amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing
30 the resulting variants for activity (such as in any of the *in vitro* assays described herein) for activity exhibited by the full-length or mature polypeptide sequence.

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LP polypeptide fragments are also provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length or native protein.

- 5 Certain fragments contemplated by the present invention may lack amino acid residues that are not essential for a desired biological activity of the LP polypeptide.

- LP polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide
10 fragments may be chemically synthesized. An alternative approach involves generating LP fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable
15 restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment by polymerase chain reaction (PCR). Oligonucleo-
20 tides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, LP polypeptide fragments share at least one biological and/or immunological activity with at least one of the LP polypeptides as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or
25 38.

- Covalent modifications of LP polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an LP polypeptide with an organic derivatizing agent
30 that is capable of reacting with selected side chains or the N- or C-terminal residues of an LP polypeptide. Derivatization with bifunctional agents is useful, for

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instance, for crosslinking LP polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-LP polypeptide antibodies, and vice-versa. Commonly used crosslinking agents include, e.g.,

5 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis-(succinimidylpropionate), bifunctional maleimides such as

10 bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithiolpropionimide].

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline

15 and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains [Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the

20 N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the LP polypeptides included within the scope of this invention comprises altering the native glycosylation pattern of the

25 polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence LP polypeptide and/or adding one or more glycosylation sites that are not present in the native sequences of LP

30 polypeptides. Additionally, the phrase includes qualitative changes in the glycosylation of the native

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proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to LP polypeptides may be accomplished by altering the amino acid sequence

5 thereof. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequences of LP polypeptides (for O-linked glycosylation sites). The LP amino acid sequences may optionally be altered through
10 changes at the DNA level, particularly by mutating the DNA encoding the LP polypeptides at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate
15 moieties on the LP polypeptides is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, pp. 259-306 (1981).

20 Removal of carbohydrate moieties present on the LP polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art
25 and described, for instance, by Sojar, et al., *Arch. Biochem. Biophys.* 259:52-7 (1987), and by Edge, et al., *Anal. Biochem.* 118:131-7 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as
30 described by Thotakura, et al., *Meth. Enzymol.* 138:350-9 (1987).

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Another type of covalent modification of LP comprises linking any one of the LP polypeptides to one of a variety of non-proteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) in the manner
5 set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192, or 4,179,337.

LP polypeptides of the present invention may also be modified in a way to form chimeric molecules comprising an LP polypeptide fused to another heterologous polypeptide or
10 amino acid sequence. In one embodiment, such a chimeric molecule comprises a fusion of an LP polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of
15 LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide. The presence of such epitope-tagged forms of an LP polypeptide can be detected using an antibody against
20 the tag polypeptide. Also, provision of the epitope tag enables an LP polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag.

In an alternative embodiment, the chimeric molecule
25 may comprise a fusion of an LP polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule, such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble
30 transmembrane domain deleted or inactivated form of an LP polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment,

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the immunoglobulin fusion includes the hinge, CH2 and CH3 or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions, see also U.S. Patent 5,428,130.

5 In yet a further embodiment, the LP polypeptides of the present invention may also be modified in a way to form a chimeric molecule comprising an LP polypeptide fused to a leucine zipper. Various leucine zipper polypeptides have been described in the art. See, e.g., Landschulz, et al.,
10 *Science* 240(4860):1759-64 (1988); WO 94/10308; Hoppe, et al., *FEBS Letters* 344(2-3):191-5 (1994); Abel, et al., *Nature* 341(6237):24-5 (1989). It is believed that use of a leucine zipper fused to an LP polypeptide may be desirable to assist in dimerizing or trimerizing soluble LP
15 polypeptide in solution. Those skilled in the art will appreciate that the zipper may be fused at either the N- or C-terminal end of an LP polypeptide.

The description below relates primarily to production of LP polypeptides by culturing cells transformed or
20 transfected with a vector containing an LP polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare LP polypeptides. For instance, the LP polypeptide sequence, or portions thereof, may be
25 produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart, et al., *Solid-Phase Peptide Synthesis*, W.H. Freeman & Co., San Francisco, CA (1969); Merrifield, *J. Am. Chem. Soc.* 85:2149-2154 (1963)]. In vitro protein synthesis may be performed using manual
30 techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's

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instructions. Various portions of an LP polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce a full-length LP polypeptide.

5 DNA encoding an LP polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the LP polypeptide-encoding mRNA and to express it at a detectable level. Libraries can be screened with probes (such as antibodies to an LP polypeptide or
10 oligonucleotides of at least about 20 to 80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook, et al., *Molecular Cloning: A
15 Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY (1989). An alternative means to isolate the gene encoding an LP polypeptide is to use PCR methodology [Sambrook, et al., supra; Dieffenbach, et al., *PCR Primer: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY (1995)].

20 Nucleic acids having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time and, if necessary, using conventional primer extension procedures as described in Sambrook, et al.,
25 supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

Host cells are transfected or transformed with expression or cloning vectors described herein for LP polypeptide production and cultured in conventional
30 nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions,

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such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in *Mammalian Cell Biotechnology: A Practical Approach*, Butler, ed. (IRL Press, 1991) and Sambrook, et al., supra. Methods of transfection are known to the ordinarily skilled artisan, for example, calcium phosphate and electroporation. General aspects of mammalian cell host system transformations have been described in U.S. Patent 4,399,216. Transformations into yeast are typically carried out according to the method of van Solingen, et al., *J Bact.* 130(2):946-7 (1977) and Hsiao, et al., *Proc. Natl. Acad. Sci. USA* 76(8):3829-33 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene or polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown, et al., *Methods in Enzymology* 185:527-37 (1990) and Mansour, et al., *Nature* 336(6197):348-52 (1988).

Suitable host cells for cloning or expressing the nucleic acid (e.g., DNA) in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* strain X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*,

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Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e.g., Salmonella typhimurium, Serratia, e.g., Serratia marcescans, and Shigella, as well as Bacilli such as B. subtilis and B. licheniformis (e.g., B. licheniformis 41P disclosed in DD 266,710, published 12 April 1989), Pseudomonas such as P. aeruginosa, and Streptomyces. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3 110 may be modified to effect a genetic mutation in a gene encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype tonAD; *E. coli* W3110 strain 9E4, which has the complete genotype tonAD ptr3; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype tonAD ptr3 phoADE15 D(argF-lac)169 ompTD degP41kan^{R'}; *E. coli* W3110 strain 37D6, which has the complete genotype tonAD ptr3 phoADE15 D(argF-lac)169 ompTD degP41kan^R rbs7D ilvG; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant degP deletion mutation; and an *E. coli* strain having mutant periplasmic protease as disclosed in U.S. Patent 4,946,783 issued 7 August 1990. Alternatively, *in vivo* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for LP vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* [Beach and Nurse,

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Nature 290:140-3 (1981); EP 139,383 published 2 May 1995]; *Muyveromyces* hosts [U.S. Patent 4,943,529 Fleer, et al., *Bio/Technology* 9(10):968-75 (1991)] such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574) [de Louvencourt, et al., *J. Bacteriol.* 154(2):737-42 (1983)]; *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906) [Van den Berg, et al., *Bio/Technology* 8(2):135-9 (1990)]; *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070) [Sreekrishna, et al., *J. Basic Microbiol.* 28(4):265-78 (1988)]; *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa* [Case, et al., *Proc. Natl. Acad. Sci. USA* 76(10):5259-63 (1979)]; *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* [Ballance, et al., *Biochem. Biophys. Res. Comm.* 112(1):284-9 (1983); Tilburn, et al., *Gene* 26(2-3):205-21 (1983); Yelton, et al., *Proc. Natl. Acad. Sci. USA* 81(5):1470-4 (1984)] and *A. niger* [Kelly and Hynes, *EMBO J.* 4(2):475-9 (1985)]. Methylotrophic yeasts are selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeast may be found in Antony, *The Biochemistry of Methylotrophs* 269 (1982).

Suitable host cells for the expression of glycosylated LP polypeptides are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sp, *Spodoptera* high5 as well as plant cells. Examples of useful mammalian host cell

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lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line [293 or 293 cells subcloned for growth in suspension culture, Graham, et al., *J. Gen Virol.*, 36(1):59-74 (1977)]; Chinese hamster ovary cells/-DHFR [CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77(7):4216-20 (1980)]; mouse sertoli cells [TM4, Mather, *Biol. Reprod.* 23(1):243-52 (1980)]; human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

LP polypeptides may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the LP polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* cc-factor leaders, the latter described in U.S. Patent 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179), or the signal described in WO 90/13646. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal

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sequences from secreted polypeptides of the same or related species as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the LP polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77(7):4216-20 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb, et al., *Nature* 282(5734):39-43 (1979); Kingsman, et al., *Gene* 7(2):141-52 (1979); Tschumper, et al., *Gene* 10(2):157-66 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of

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yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEPC1 [Jones, *Genetics* 85:23-33 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the LP polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the P-lactamase and lactose promoter systems [Chang, et al., *Nature* 275(5681):617-24 (1978); Goeddel, et al., *Nature* 281(5732):544-8 (1979)], alkaline phosphatase, a tryptophan (up) promoter system [Goeddel, *Nucleic Acids Res.* 8(18):4057-74 (1980); EP 36,776 published 30 September 1981], and hybrid promoters such as the tat promoter [deBoer, et al., *Proc. Natl. Acad. Sci. USA* 80(1):21-5 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding LP polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman, et al., *J. Biol. Chem.* 255(24):12073-80 (1980)] or other glycolytic enzymes [Hess, et al., *J. Adv. Enzyme Reg.* 7:149 (1968); Holland, *Biochemistry* 17(23):4900-7 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol

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dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657. LP transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a polynucleotide encoding an LP polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, alpha-ketoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the LP polypeptide coding sequence but is preferably located at a site 5' from the promoter.

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Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and occasionally 3' untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding LP.

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, *Proc. Natl. Acad. Sci. USA* 77(9):5201-5 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a

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native sequence provided herein or against exogenous sequence fused to an LP polypeptide-encoding DNA and encoding a specific antibody epitope.

Various forms of an LP polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g., Triton X-100TM) or by enzymatic cleavage. Cells employed in expression of an LP polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desirable to purify LP polypeptides from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reversed-phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex[®] G-75; protein A Sepharose[®] columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of an LP polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, *Methods in Enzymology* 182:83-9 (1990) and Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag, NY (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular LP polypeptide produced.

Nucleotide sequences (or their complement) encoding LP polypeptides have various applications in the art of molecular biology, including uses as hybridization probes,

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in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. LP polypeptide-encoding nucleic acids will also be useful for the preparation of LP polypeptides by the recombinant techniques described
5 herein.

The full-length LP polypeptide-encoding nucleotide sequence (e.g., SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37), or portions thereof, may be useful as hybridization probes for probing
10 a cDNA or genomic library to isolate the full-length LP polypeptide-encoding cDNA or genomic sequences including promoters, enhancer elements and introns of native sequence LP polypeptide-encoding DNA or to isolate still other genes (for instance, those encoding naturally-occurring variants
15 of LP polypeptides or the same from other species) which have a desired sequence identity to the LP polypeptide-encoding nucleotide sequence disclosed in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37. Hybridization techniques are well known in the
20 art and some of which are described in further detail in the Examples below.

Other useful fragments of the LP polypeptide-encoding nucleic acids include anti-sense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either
25 RNA or DNA) capable of binding to target LP polypeptide-encoding mRNA (sense) of LP polypeptide-encoding DNA (anti-sense) sequences. Anti-sense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of LP polypeptide-encoding DNA. Such a
30 fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an anti-sense or a sense oligonucleotide, based upon

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a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen, *Cancer Res.* 48(10):2659-68 (1988) and van der Krol, et al., *Bio/Techniques* 6(10):958-76 (1988).

5 Binding of anti-sense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of
10 transcription or translation, or by other means. The anti-sense oligonucleotides thus may be used to block expression of LP mRNA and therefore any LP polypeptide encoded thereby. Anti-sense or sense oligonucleotides further comprise oligonucleotides having modified sugar-
15 phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation)
20 but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or anti-sense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in
25 WO 90/10448, and other moieties that increase affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-L-lysine. Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or anti-sense
30 oligonucleotides to modify binding specificities of the anti-sense or sense oligonucleotide for the target nucleotide sequence.

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Anti-sense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, calcium phosphate-mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an anti-sense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MSV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated CDTSA, CTSB and DCTSC (see WO 90/13641).

Alternatively, a sense or an anti-sense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or anti-sense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

When the amino acid sequence for an LP polypeptide encodes a protein which binds to another protein (for example, where the LP polypeptide functions as a receptor), the LP polypeptide can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor LP polypeptide can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of the LP polypeptides

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disclosed herein or a receptor for such LP polypeptides. Typical screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule
5 drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well
10 characterized in the art.

Nucleic acids which encode an LP polypeptide of the present invention or any of its modified forms can also be used to generate either transgenic animals or "knockout" animals which, in turn, are useful in the development and
15 screening of therapeutically useful reagents. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patents 4,736,866 and 4,870,009. Typically, particular cells would be targeted
20 for an LP transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding an LP polypeptide.
25 Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the
30 pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

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Alternatively, non-human homologs of LP polynucleotides can be used to construct a "knockout" animal which has a defective or altered gene encoding a particular LP polypeptide as a result of homologous recombination between the endogenous gene encoding the LP polypeptide and the altered genomic DNA introduced into an embryonic cell of the animal. For example, cDNA encoding an LP polypeptide can be used to clone genomic DNA encoding that LP polypeptide in accordance with established techniques. A portion of the genomic DNA encoding an LP polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see, e.g., Thomas and Capecchi, *Cell* 51(3):503-12 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation), and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see, e.g., Li, et al., *Cell* 69(6):915-26 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see, e.g., Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed., pp. 113-152 (IRL, Oxford, 1987)]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knockout" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals

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can be characterized, for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the native LP polypeptide.

5 Transgenic non-human mammals are useful as an animal models in both basic research and drug development endeavors. Transgenic animals expressing at least one LP polypeptide or nucleic acid can be used to test compounds or other treatment modalities which may prevent, suppress, or
10 cure a pathology or disease associated with at least one of the above mentioned activities. Such transgenic animals can also serve as a model for the testing of diagnostic methods for those same diseases. Furthermore, tissues derived from such transgenic non-human mammals are useful as a source of
15 cells for cell culture in efforts to develop *in vitro* bioassays to identify compounds that modulate LP polypeptide activity or LP polypeptide dependent signaling. Accordingly, another aspect of the present invention contemplates a method of identifying compounds efficacious
20 in the treatment of at least one previously described disease or pathology associated with an LP polypeptide associated activity. A non-limiting example of such a method comprises:

- a) generating a transgenic non-human animal which
25 expresses an LP polypeptide of the present invention and which is, as compared to a wild-type animal, pathologically distinct in some detectable or measurable manner from wild-type version of said non-human mammal;
- b) exposing said transgenic animal to a compound, and;
- 30 c) determining the progression of the pathology in the treated transgenic animal, wherein an arrest, delay, or reversal in disease progression in transgenic animal treated

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with said compound as compared to the progression of the pathology in an untreated control animals is indicative that the compound is useful for the treatment of said pathology.

Another embodiment of the present invention provides a method of identifying compounds capable of inhibiting LP polypeptide activity *in vivo* and/or *in vitro* wherein said method comprises:

a) administering an experimental compound to an LP polypeptide expressing transgenic non-human animal, or tissues derived therefrom, exhibiting one or more physiological or pathological conditions attributable to the expression of an LP transgene; and

b) observing or assaying said animal and/or animal tissues to detect changes in said physiological or pathological condition or conditions.

Another embodiment of the invention provides a method for identifying compounds capable of overcoming deficiencies in LP polypeptide activity *in vivo* or *in vitro* wherein said method comprises:

a) administering an experimental compound to an LP polypeptide expressing transgenic non-human animal, or tissues derived therefrom, exhibiting one or more physiological or pathological conditions attributable to the disruption of the endogenous LP polypeptide-encoding gene; and

b) observing or assaying said animal and/or animal tissues to detect changes in said physiological or pathological condition or conditions.

Various means for determining a compound's ability to modulate the activity of an LP polypeptide in the body of the transgenic animal are consistent with the invention. Observing the reversal of a pathological condition in the LP

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polypeptide expressing transgenic animal after administering a compound is one such means. Another more preferred means is to assay for markers of LP activity in the blood of a transgenic animal before and after administering an experimental compound to the animal. The level of skill of an artisan in the relevant arts readily provides the practitioner with numerous methods for assaying physiological changes related to therapeutic modulation of LP activity.

- 10 "Gene therapy" includes both conventional gene therapy, where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA.
- 15 Anti-sense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short anti-sense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane [Zamecnik, *et al.*, *Proc. Natl. Acad Sci. USA* 83(12):4143-6 (1986)]. The oligonucleotides can be modified to enhance their uptake, e.g., by substituting their negatively charged phosphodiester groups with uncharged groups.
- 25 There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cell *in vitro* or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro*
- 30 include the use of liposomes, electroporation, micro-injection, cell fusion, DEAE-dextran, the calcium phosphate

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precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically, retroviral) vectors and viral coat protein-liposome mediated transfection [Dzau, et al., *Trends in Biotechnology* 11(5):205-10 (1993)]. In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cells, etc.

Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g., capsid proteins or fragments thereof trophic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu, et al., *J. Biol. Chem.* 262(10):4429-32 (1987); and Wagner, et al., *Proc. Natl. Acad. Sci. USA* 87(9):3410-4 (1990). For a review of gene marking and gene therapy protocols, see Anderson, *Science* 256(5058):808-13 (1992).

The nucleic acid molecules encoding LP polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data, are presently available. Each LP polypeptide-encoding nucleic acid molecule of the present invention can be used as a chromosome marker. An LP polypeptide-encoding nucleic acid or fragments thereof can

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also be used for chromosomal localization of the gene encoding that LP polypeptide.

The present invention further provides anti-LP polypeptide antibodies. Exemplary antibodies include
5 polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

The anti-LP polypeptide antibodies of the present invention may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled
10 artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal
15 injections. The immunizing agent may include the LP polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to,
20 keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization
25 protocol may be selected by one skilled in the art without undue experimentation.

The anti-LP polypeptide antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described
30 by Kohler and Milstein, *Nature* 256(5517):495-7 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an immunizing agent

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to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

5 The immunizing agent will typically include an LP polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used, if cells of human origin are desired, or spleen cells or lymph node cells are used, if non-human mammalian sources are desired.

10 The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, pp. 59-103 (1986)]. Immortalized cell lines are usually

15 transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or

20 survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"),

25 which prevents the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred

30 immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, CA, and the American Type

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Culture Collection (ATCC), Rockville, MD. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, *J. Immunol.* 133(6):3001-5 (1984); Brodeur, et al.,
5 *Monoclonal Antibody Production Techniques and Applications*, Marcel Dekker, Inc., NY, pp. 51-63 (1987)].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against an LP polypeptide. Preferably,
10 the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding
15 affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Rodbard, *Anal. Biochem.* 107(1):220-39 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and
20 grown by standard methods [Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press, pp. 59-103 (1986)]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be
25 grown *in vivo* as ascites in a mammal.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced
30 using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains

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of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian
5 COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human
10 heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent 4,816,567; Morrison, et al., *Proc. Natl. Acad. Sci. USA* 81(21):6851-5 (1984)] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a
15 non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent
20 antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy
25 chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

30 *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce

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fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

The anti-LP polypeptide antibodies of the invention may further comprise humanized antibodies or human
5 antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human
10 immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary-determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the
15 desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported
20 CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of
25 the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones, et al., *Nature* 321(6069):522-5
30 (1986); Riechmann, et al., *Nature* 332(6162):323-7 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-6 (1992)].

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Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones, et al., *Nature* 321(6069):522-5 (1986); Riechmann, et al., *Nature* 332(6162):323-7 (1988); Verhoeyen, et al., *Science* 239(4847):1534-6 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, *J. Mol. Biol.* 227(2):381-8 (1992); Marks, et al., *J. Mol. Biol.* 222(3):581-97 (1991)]. The techniques of Cole, et al., and Boerner, et al., are also available for the preparation of human monoclonal antibodies (Cole, et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985), and Boerner, et al., *J. Immunol.* 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been

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partially or complete inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly and antibody repertoire. This approach is described, for example, in U.S. Patents 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks, et al., *Biotechnology* 10(7):779-83 (1992); Lonberg, et al., *Nature* 368(6474):856-9 (1994); Morrison, *Nature* 368(6474):812-3 (1994); Fishwild, et al., *Nature Biotechnology* 14(7):845-51 (1996); Neuberger, *Nature Biotechnology* 14(7):826 (1996); Lonberg and Huszar, *Int. Rev. Immunol.* 13(1):65-93 (1995).

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an LP polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit. Methods for making bispecific antibodies are known in the art. Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared [Tutt, et al., *J Immunol.* 147(1):60-9 (1991)].

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/20373]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving

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crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-
5 mercaptobutyrimidate and those disclosed, for example, in U.S. Patent 4,676,980.

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically
10 active toxin of bacterial, fungal, plant or animal origin, or fragments thereof, or a small molecule toxin), or a radioactive isotope (i.e., a radioconjugate).

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein coupling
15 agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds,
20 bis-diazonium derivatives (such as bis-2-diazoniumbenzoyl)-ethylenediamine) diisocyanates (such as tolylene-2,6-diisocyanate), and bioactive fluorine compounds. For example, a ricin immunotoxin can be prepared as described in Vitetta, et al., *Science* 238(4830):1098-104 (1987).
25 Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody.

In another embodiment, the antibody may be conjugated
30 to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of

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unbound conjugate from the circulation using a clearing agent, and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

5 The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Eppstein, et al., *Proc. Natl. Acad. Sci. USA* 82:3688-92 (1985); Hwang, et al., *Proc. Natl. Acad. Sci. USA*
10 77(7):4030-4 (1980); and U.S. Patents 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition
15 comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the
20 liposomes as described in Martin, et al., *J. Biol. Chem.* 257(1):286-8 (1982) via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon, et al., *J. National Cancer Inst.* 81(19):484-8 (1989).

25 Antibodies specifically binding an LP polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

30 If an LP polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also

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be used to deliver the antibody or an antibody fragment into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For
5 example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco, et al.,
10 *Proc. Natl. Acad. Sci. USA* 90(16):7889-93 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other.
15 Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokines, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitable present in combination in amounts that are effective for
20 the purpose intended. The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methacrylate) microcapsules, respectively, in colloidal drug delivery systems (for
25 example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition (1980).
30 The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

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Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol), polylactides (U.S. Patent 3,773,919), copolymers of L-glutamic acid gamma-ethyl-L-glutamate, non-degradable ethylene-vinylacetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 degrees C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanisms involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thiosulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

The anti-LP polypeptide antibodies of the present invention have various utilities. For example, such antibodies may be used in diagnostic assays for LP

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polypeptide expression, e.g., detecting expression in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich
5 assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, *Monoclonal Antibodies: A Manual of Techniques*, CRC Press, Inc., pp. 147-158 (1987)]. The antibodies used in the assays can be labeled with a detectable moiety. The detectable moiety
10 should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or
15 luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter, et al., *Nature* 144:945 (1962); David, et al., *Biochemistry* 13(5):1014-21 (1974); Pain, et al., *J Immunol. Meth.*, 40(2):219-30 (1981); and Nygren, *J. Histochem. Cytochem.* 30(5):407-12 (1982).

Anti-LP polypeptide antibodies also are useful for affinity purification from recombinant cell culture or
25 natural sources. In this process, the antibodies are immobilized on a suitable support, such a Sephadex[®] resin or filter paper, using methods well known in the art. The immobilized antibody is then contacted with a sample containing the LP polypeptide to be purified, and
30 thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the LP polypeptide, which is bound to the

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immobilized antibody. Finally, the support is washed with another suitable solvent that will release the desired polypeptide from the antibody.

This invention encompasses methods of screening compounds to identify those that mimic the activity of the LP polypeptide (agonists) disclosed herein or prevent the effects of the LP polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with an LP polypeptide encoded by the genes identified herein or otherwise interfere with the interaction of LP polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats. In binding assays, the interaction is binding, and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, an LP polypeptide encoded by a gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution comprising LP polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by

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washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to an LP polypeptide, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers [Fields and Song, *Nature* 340(6230):245-6 (1989); Chien, et al., *Proc. Natl. Acad. Sci. USA* 88(21):9578-82 (1991); Chevray and Nathans, *Proc. Natl. Acad. Sci. USA* 89(13):5789-93 (1992)]. Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, while the other functions as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another in which candidate activating proteins are fused to

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the activation domain. The expression of GAL1-lacZ reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with chromogenic substrate for beta-galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of an LP polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture to serve as a positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

Antagonists may be detected by combining at least one LP polypeptide and a potential antagonist with a membrane-

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bound or recombinant receptor for that LP polypeptide under appropriate conditions for a competitive inhibition assay. The LP polypeptide can be labeled, such as by radioactivity, such that the number of LP polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor for an LP polypeptide can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. See Coligan, et al., *Current Protocols in Immunology* 1(2):Ch. 5 (1991). Preferably, expression cloning is employed such that polyadenylated mRNA is prepared from a cell responsive to the secreted form of a particular LP polypeptide, and a cDNA library created from this mRNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the secreted LP polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled LP polypeptide. The LP polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, a labeled LP polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into

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peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify
5 the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with a labeled LP polypeptide in the presence of the candidate compound. The ability of the compound to
10 enhance or block this interaction could then be removed.

Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the LP polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the
15 polypeptide.

Another potential LP antagonist is an anti-sense RNA or DNA construct prepared using anti-sense technology, where, e.g., an anti-sense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to
20 targeted mRNA and prevent its translation into protein. Anti-sense technology can be used to control gene expression through triple-helix formation or anti-sense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding
25 portion of the polynucleotide sequence, which encodes the mature form of an LP polypeptide can be used to design an anti-sense RNA oligonucleotide sequence of about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in
30 transcription [triple helix; see Lee, et al., *Nucl. Acids Res* 6(9):3073-91 (1979); Cooney, et al., *Science* 241(4864):456-9 (1988); Beal and Dervan, *Science*

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251(4999):1360-3 (1991)], thereby preventing transcription and production of the LP polypeptide. The anti-sense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecules [anti-sense; see Okano, 5 *J. Neurochem.* 56(2):560-7 (1991); *Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression* (CRC Press: Boca Raton, FL 1988)]. The oligonucleotides described above can also be delivered to cells such that the anti-sense RNA or DNA may be expressed *in vivo* to inhibit production of the 10 LP polypeptide. When anti-sense DNA is used, oligodeoxy-ribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that 15 bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the LP polypeptide, thereby blocking the normal biological activity of the LP polypeptide. Examples of small molecules include, but are not limited to, small peptides 20 or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target 25 RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details, see, e.g., Rossi, *Current Biology* 4(5):469-71 (1994) and PCT publication No. WO 97/33551 (published September 18, 30 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and

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composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details
5 see, e.g., PCT publication No. WO 97/33551, supra.

Another use of the compounds of the invention (e.g., LP polypeptides, fragments and variants thereof and LP antibodies directed thereto) described herein is to help
10 diagnose whether a disorder is driven to some extent by the modulation of signaling by an LP polypeptide

A diagnostic assay to determine whether a particular disorder is driven by LP polypeptide dependent signaling can be carried out using the following steps:

- 15 a) culturing test cells or tissues expressing an LP polypeptide;
- b) administering a compound which can inhibit LP polypeptide dependent signaling; and
- c) measuring LP polypeptide mediated phenotypic effects
20 in the test cells.

The steps can be carried out using standard techniques in light of the present disclosure. Appropriate controls take into account the possible cytotoxic effect of a compound, such as treating cells not associated with a cell
25 proliferative disorder (e.g., control cells) with a test compound and can also be used as part of the diagnostic assay. The diagnostic methods of the invention involve the screening for agents that modulate the effects of LP polypeptide-associated disorders.

30 The LP polypeptides or antibodies thereto as well as LP polypeptide antagonists or agonists can be employed as therapeutic agents. Such therapeutic agents are formulated

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according to known methods to prepare pharmaceutically useful compositions, whereby the LP polypeptide or antagonist or agonist thereof is combined in a mixture with a pharmaceutically acceptable carrier.

5 In the case of LP polypeptide antagonistic or agonistic antibodies, if the LP polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the
10 antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment which specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable region sequences of an antibody, peptide
15 molecules can be designed which retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology [see, e.g., Marasco, et al., *Proc. Natl. Acad. Sci. USA* 90(16):7889-93 (1993)].

20 Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers [*Remington's Pharmaceutical Sciences* 16th edition (1980)], in the form of lyophilized
25 formulations or aqueous solutions.

 The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such
30 molecules are suitably present in combination in amounts that are effective for the purpose intended.

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The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-
5 (methacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences, supra*.

10 The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example,
15 and intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers
20 containing the therapeutic agent(s), which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels [for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)], polylactides, copolymers of L-
25 glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid
copolymer and leuprolide acetate), and poly-D-(-)-3-
30 hydroxybutyric acid. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon, and

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interleukin-2. Johnson, et al., *Nat. Med.* 2(7):795-9 (1996); Yasuda, et al., *Biomed. Ther.* 27:1221-3 (1993); Hora, et al., *Bio/Technology* 8(8):755-8 (1990); Cleland, "Design and Production of Single Immunization Vaccines
5 Using Polylactide Polyglycolide Microsphere Systems" in *Vaccine Design: The Subunit and Adjuvant Approach*, Powell and Newman, Eds., Plenum Press, NY, 1995, pp. 439-462
WO 97/03692; WO 96/40072; WO 96/07399; and U.S. Patent 5,654,010.

10 The sustained-release formulations of these proteins may be developed using polylactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly
15 within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. See Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer" in *Biodegradable Polymers as
20 Drug Delivery Systems* (Marcel Dekker; New York, 1990), M. Chasin and R. Langer (Eds.) pp. 1-41.

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for
25 shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 degrees C, resulting in a loss of biological activity and possible changes in immunogenicity.

30 It is contemplated that the compounds, including, but not limited to, antibodies, small organic and inorganic molecules, peptides, anti-sense molecules, ribozymes, etc.,

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of the present invention may be used to treat various conditions including those characterized by overexpression and/or activation of the disease-associated genes identified herein. The active agents of the present
5 invention (e.g., antibodies, polypeptides, nucleic acids, ribozymes, small organic or inorganic molecules) are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by
10 intramuscular, intraperitoneal, intracerebral, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, intraocular, intralesional, oral, topical, inhalation, pulmonary, and/or through sustained release.

15 Other therapeutic regimens may be combined with the administration of LP polypeptide antagonists or antagonists, anti-cancer agents, e.g., antibodies of the instant invention.

For the prevention or treatment of disease, the
20 appropriate dosage of an active agent, (e.g., an antibody, polypeptide, nucleic acid, ribozyme, or small organic or inorganic molecule) will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the agent is administered for
25 preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the agent, and the discretion of the attending physician. The agent is suitably administered to the patient at one time or over a series of treatments.

30 Dosages and desired drug concentration of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The

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determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective doses for human therapy.

- 5 Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti and Chappell, "The Use of Interspecies Scaling in Toxicokinetics," in *Toxicokinetics and New Drug Development*, Yacobi, et al., Eds., Pergamon Press, NY, 10 p.4246 (1989).

When *in vivo* administration of a composition comprising an LP polypeptide, an LP polypeptide antibody, an LP polypeptide-encoding nucleic acid, ribozyme, or small organic or inorganic molecule is employed, normal dosage 15 amounts may vary from about 1 ng/kg up to 100 mg/kg of mammal body weight or more per day, preferably about 1 pg/kg/day up to 100 mg/kg of mammal body weight or more per day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery 20 is provided in the literature; see, for example, U.S. Patents 4,657,760, 5,206,344 or 5,225,212. It is within the scope of the invention that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one 25 organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue. Moreover, dosages may be administered by one or more separate administrations or by continuous infusion. For repeated administrations over several days or longer, 30 depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress

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of this therapy is easily monitored by conventional techniques and assays.

In another embodiment of the invention, an article of manufacture containing materials useful for the diagnosis or treatment of the disorders described above is provided. The article of manufacture comprises a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for diagnosing or treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is typically an LP polypeptide, antagonist or agonist thereof. The label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

In another embodiment of the invention, therapeutic utility of the LP polypeptide is determined by measuring phosphorylation of tyrosine residues on specific cell lines. The early cellular response of cells stimulated with the majority of proteins is protein phosphorylation of the tyrosine residues. This response includes autophosphorylation of corresponding receptors, which thereby leads

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to the activation of catalytic properties and the initiation of intracellular pathways specific to the cell type. Moreover, signaling downstream of receptors requires phosphorylation of specific kinases inside the cell and
5 other intracellular enzymes of different origin as well as the phosphorylation of multiple adapter/scaffold, structural proteins and transcriptional factors. Therefore, diverse protein-induced cell responses can be visualized by monitoring the state of protein
10 phosphorylation after cell stimulation.

Immunodetection is used to detect the protein phosphorylation of the stimulated cell. Several antibodies that are directed against specific phosphorylated epitopes in signaling molecules are readily available. Two specific
15 antibodies are used: phosphospecific anti-MAPK and anti-AKT antibodies. Additionally, non-specific anti-phosphotyrosine antibodies, which recognize tyrosine-phosphorylated proteins, are used. While anti-phosphotyrosine antibodies allow detection of diverse tyrosine phosphorylated proteins
20 without directly addressing the nature of their identity, the phosphospecific anti-MAPK and anti-AKT antibodies recognize only the corresponding proteins in their phosphorylated form.

Another assay to determine utility of LP polypeptides
25 involves transfection of cell lines with reporter plasmids followed by cell stimulation with an LP polypeptide. Each reporter consists of a defined element, responsive to specific intracellular signaling pathways, upstream of a sequence involving a reporter protein such as luciferase.
30 Upon stimulation of the element, reporter transcription and translation ensues, and the resulting protein levels can be detected using an assay such as a luminescence assay. The

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cell stimulation period depends on the reporter plasmid used.

For each reporter used, positive controls are designed in the form of agonist cocktails which include approximately
5 maximal stimulatory doses of several ligands known to stimulate the represented signaling pathway. Using this design, the chances of finding a positive stimulus for each cell line is maximized. The caveat, however, is that some cell line / reporter combinations will not be stimulated by
10 the specific agonist cocktail, due to lack of an appropriate ligand in the cocktail. Alternately, the lack of signal induction by an agonist cocktail may be the lack of all signaling components within a particular cell line to activate the transcriptional element. Cell line / reporter
15 combinations with no exogenous stimulus added make up the negative controls.

Another assay to determine utility of LP polypeptides involves transfection of cell lines with reporter plasmids followed by cell stimulation with an LP polypeptide. Each
20 reporter consists of a defined element, responsive to specific intracellular signaling pathways, upstream of a sequence involving a reporter protein such as luciferase. Upon stimulation of the element, reporter transcription and translation ensues, and the resulting protein levels can be
25 detected using an assay such as a luminescence assay. The cell stimulation period depends on the reporter plasmid used.

For each reporter used, positive controls are designed in the form of agonist cocktails which include
30 approximately maximal stimulatory doses of several ligands known to stimulate the represented signaling pathway. Using this design, the chances of finding a positive

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stimulus for each cell line is maximized. The caveat, however, is that some cell line/reporter combinations will not be stimulated by the specific agonist cocktail, due to lack of an appropriate ligand in the cocktail.

- 5 Alternately, the lack of signal induction by an agonist cocktail may be the lack of all signaling components within a particular cell line to activate the transcriptional element. Cell line / reporter combinations with no exogenous stimulus added make up the negative controls.

- 10 In another assay, utility of LP polypeptide is determined by proliferation of cells. In this assay, gross changes in the number of cells remaining in a culture are monitored after exposure to an LP polypeptide for three days. The cells are incubated in an appropriate assay
15 medium to produce a sub-optimal growth rate. For example, usually a 1:10 or 1:20 dilution of normal culture medium results in a 40 to 60% reduction in cell number compared to the undiluted culture medium. This broad growth zone is chosen so that if an LP polypeptide is a stimulator of
20 growth, the cells have room to expand, and conversely, if the LP polypeptide is deleterious, a reduction in cell density can be detected. After a period of exposure, the assay media is replaced with media containing a detection agent such as Calcein AM, a membrane-permeant fluorescent
25 dye, allowing quantification of the cell number.

- For use in another assay, a FLAG-HIS (FLIS)-tagged version of the LP polypeptide is expressed using mammalian cells such as HEK-293EBNA, COS-7, or HEK293T. The coding region of the cDNA is amplified by PCR of a vector
30 containing a fragment encoding the LP polypeptide. The PCR-generated fragment is cleaved with restriction enzymes and gel-purified. The fragment is then ligated into a

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mammalian expression vector containing the FLIS epitope tag fused to the C-terminus. Protein expressed by this plasmid construct includes both the FLAG tag (Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys) and the 6X His tag at the COOH -terminus of the protein. This tag provides epitopes for commercially available tag-specific antibodies, enabling detection of the protein.

To determine expression of the LP polypeptide in tissues, a protein-binding assay is performed. The fixed tissue sample is exposed to the FLIS-tagged LP polypeptide, followed by exposure to a primary antibody and a secondary antibody containing a fluorescent dye. Tagged LP polypeptide that binds to the antigens in the tissue will fluoresce. Binding of the protein to an antigen in the tissue suggests that the protein is expressed in that tissue. Thus, protein expression can be determined by measuring which tissues fluoresce.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

EXAMPLES

Example 1

25 Expression and Purification of LP polypeptides in *E. coli*

The bacterial expression vector pQE60 is used for bacterial expression in this example. (QIAGEN, Inc., Chatsworth, CA). pQE60 encodes ampicillin antibiotic resistance ("Amp^r") and contains a bacterial origin of replication ("ori"), an IPTG inducible promoter, a ribosome binding site ("RBS"), six codons encoding histidine residues that allow affinity purification using nickel-nitrilo-

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triacetic acid ("Ni-NTA") affinity resin sold by QIAGEN, Inc., and suitable single restriction enzyme cleavage sites. These elements are arranged such that a DNA fragment encoding a polypeptide can be inserted in such a way as to
5 produce that polypeptide with the six His residues (i.e., a "6 X His tag") covalently linked to the carboxyl terminus of that polypeptide. However, a polypeptide coding sequence can optionally be inserted such that translation of the six His codons is prevented and, therefore, a polypeptide is
10 produced with no 6 X His tag.

The nucleic acid sequence encoding the desired portion of an LP polypeptide lacking the hydrophobic leader sequence is amplified from a cDNA clone using PCR oligonucleotide primers (based on the sequences presented, e.g., in SEQ ID
15 NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37) which anneal to the amino terminal encoding DNA sequences of the desired portion of the LP polypeptide-encoding nucleic acid and to sequences in the construct 3' to the cDNA coding sequence. Additional
20 nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' sequences, respectively.

For cloning, the 5' and 3' primers have nucleotides corresponding or complementary to a portion of the coding
25 sequence of the LP polypeptide-encoding nucleic acid, e.g., as presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37, according to known method steps. One of ordinary skill in the art would appreciate, of course, that the point in a polynucleotide
30 sequence where the 5' primer begins can be varied to amplify a desired portion of the complete polypeptide-encoding

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polynucleotide shorter or longer than the polynucleotide which encodes the mature form of the polypeptide.

The amplified nucleic acid fragments and the vector pQE60 are digested with appropriate restriction enzymes, and the digested DNAs are then ligated together. Insertion of the LP polypeptide-encoding DNA into the restricted pQE60 vector places the LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) polypeptide coding region including its associated stop codon downstream from the IPTG-inducible promoter and in-frame with an initiating AUG codon. The associated stop codon prevents translation of the six histidine codons downstream of the insertion point.

The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described in Sambrook, et al., 1989; Ausubel, 1987-1998. *E. coli* strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers kanamycin resistance ("Kanr"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing LP polypeptides, is available commercially from QIAGEN, Inc. Transformants are identified by their ability to grow on LB plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 μ g/mL) and kanamycin (25 μ g/mL). The O/N culture is used to inoculate a large

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culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. Isopropyl-beta-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM to induce transcription from the lac repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for three to four hours. Cells then are harvested by centrifugation.

The cells are then stirred for three to four hours at 4 degrees C in 6 M guanidine hydrochloride, pH 8. The cell debris is removed by centrifugation, and the supernatant containing the LP polypeptide is dialyzed against 50 mM sodium acetate buffer, pH 6, supplemented with 200 mM sodium chloride. Alternatively, a polypeptide can be successfully refolded by dialyzing it against 500 mM sodium chloride, 20% glycerol, 25 mM Tris hydrochloride, pH 7.4, containing protease inhibitors.

If insoluble protein is generated, the protein is made soluble according to known method steps. After renaturation, the polypeptide is purified by ion exchange, hydrophobic interaction, and size exclusion chromatography. Alternatively, an affinity chromatography step such as an antibody column is used to obtain pure LP polypeptide. The purified polypeptide is stored at 4 degrees C or frozen at negative 40 degrees C to negative 120 degrees C.

Example 2

Cloning and Expression of LP polypeptides in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 GP is used to insert the cloned DNA encoding the mature LP polypeptide into a baculovirus, using a baculovirus leader

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and standard methods as described in Summers, et al., A
*Manual of Methods for Baculovirus Vectors and Insect Cell
Culture Procedures*, Texas Agricultural Experimental Station
Bulletin No. 1555 (1987). This expression vector contains
5 the strong polyhedrin promoter of the *Autographa californica*
nuclear polyhedrosis virus (AcMNPV) followed by the
secretory signal peptide (leader) of the baculovirus gp67
polypeptide and convenient restriction sites such as BamHI,
Xba I, and Asp718. The polyadenylation site of the simian
10 virus 40 ("SV40") is used for efficient polyadenylation.
For easy selection of recombinant virus, the plasmid
contains the beta-galactosidase gene from *E. coli* under
control of a weak *Drosophila* promoter in the same
orientation, followed by the polyadenylation signal of the
15 polyhedrin gene. The inserted genes are flanked on both
sides by viral sequences for cell-mediated homologous
recombination with wild-type viral DNA to generate viable
virus that expresses the cloned polynucleotide.

Other baculovirus vectors are used in place of the
20 vector above, such as pAc373, pVL941 and pAcIM1, as one
skilled in the art would readily appreciate, as long as the
construct provides appropriately located signals for
transcription, translation, secretion and the like,
including a signal peptide and an in-frame AUG as required.
25 Such vectors are described, for instance, in Luckow, et al.,
Virology 170:31-39.

The cDNA sequence encoding the mature LP polypeptide in
a clone, lacking the AUG initiation codon and the naturally
associated nucleotide binding site, is amplified using PCR
30 oligonucleotide primers corresponding to the 5' and 3'
sequences of the gene. Non-limiting examples include 5' and
3' primers having nucleotides corresponding or complementary

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to a portion of the coding sequence of an LP polypeptide-encoding polynucleotide, e.g., as presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37 according to known method steps.

5 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit (e.g., "Geneclean," BIO 101 Inc., La Jolla, CA). The fragment is then digested with the appropriate restriction enzyme and again is purified on a 1% agarose gel. This fragment is designated
10 herein "F1."

 The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1%
15 agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, CA). This vector DNA is designated herein "V1."

 Fragment F1 and the dephosphorylated plasmid V1 are ligated together with T4 DNA ligase. *E. coli* HB101 or other
20 suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria are identified that contain the plasmid bearing a human LP polypeptide-encoding polynucleotide using the PCR method, in
25 which one of the primers that is used to amplify the gene and the second primer is from well within the vector so that only those bacterial colonies containing an LP polypeptide-encoding polynucleotide will show amplification of the DNA. The sequence of the cloned fragment is confirmed by DNA
30 sequencing. The resulting plasmid is designated herein as pBacLP.

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Five μg of the plasmid pBacLP plasmid construct is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold[®] baculovirus DNA", PharMingen, San Diego, CA), using the lipofection method described by Felgner, et al., *Proc. Natl. Acad. Sci. USA* 84: 7413-7 (1987). 1 μg of BaculoGold[®] virus DNA and 5 μg of the plasmid pBacLP are mixed in a sterile well of a microtiter plate containing 50 μL of serum-free Grace's medium (Life Technologies, Inc., Rockville, MD).

10 Afterwards, 10 μL Lipofectin plus 90 μL Grace's medium are added, mixed and incubated for fifteen minutes at room temperature. Then, the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 mL Grace's medium without

15 serum. The plate is rocked back and forth to mix the newly added solution. The plate is then incubated for five hours at 27 degrees C. After five hours, the transfection solution is removed from the plate and 1 mL of Grace's insect medium supplemented with 10% fetal calf serum is

20 added. The plate is put back into an incubator and cultivation is continued at 27 degrees C for four days.

After four days, the supernatant is collected, and a plaque assay is performed. An agarose gel with "Blue Gal" (Life Technologies, Inc., Rockville, MD) is used to allow

25 easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies, Inc.,

30 Rockville, MD, pp. 9-10). After appropriate incubation, blue stained plaques are picked with a micropipettor tip (e.g., Eppendorf). The agar containing the recombinant

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viruses is then resuspended in a microcentrifuge tube containing 200 μ L of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later, the
5 supernatants of these culture dishes are harvested and then stored at 4 degrees C.

To verify the expression of the LP polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the
10 recombinant baculovirus at a multiplicity of infection ("MOI") of about two. Six hours later, the medium is removed and replaced with SF900 II medium minus methionine and cysteine (available, e.g., from Life Technologies, Inc., Rockville, MD). If radiolabeled polypeptides are desired,
15 42 hours later, 5 mCi of 35 S-methionine and 5 mCi 35 S-cysteine (available from Amersham, Piscataway, NJ) are added. The cells are further incubated for sixteen hours and then harvested by centrifugation. The polypeptides in the supernatant as well as the intracellular polypeptides
20 are analyzed by SDS-PAGE, followed by autoradiography (if radiolabeled). Microsequencing of the amino acid sequence of the amino terminus of purified polypeptide can be used to determine the amino terminal sequence of the mature polypeptide and, thus, the cleavage point and length of the
25 secretory signal peptide.

Example 3

Cloning and Expression of an LP Polypeptide in Mammalian Cells

30 A typical mammalian expression vector contains at least one promoter element, which mediates the initiation

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of transcription of mRNA, the polypeptide coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening
5 sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLVII, HIVI and the early promoter of the cytomegalovirus
10 (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIRESneo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech Labs, Palo Alto, CA), pCDNA3.1
15 (+/-), pCDNA/Zeo (+/-) or pCDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Other suitable mammalian host cells include human Hela 293, H9, Jurkat cells, mouse NIH3T3, C127 cells,
20 Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells, and Chinese hamster ovary (CHO) cells.

Alternatively, the gene is expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as DHFR
25 (dihydrofolate reductase), GPT neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded polypeptide. The DHFR marker
30 is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine

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synthase (GS) [Murphy, et al., *Biochem. J.* 227:277-9 (1991); Bebbington, et al., *Bio/Technology* 10:169-75 (1992)]. Using these markers, the mammalian cells are grown in selective medium and the cells with the highest
5 resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of polypeptides.

The expression vectors pC1 and pC4 contain the strong
10 promoter (LTR) of the Rous Sarcoma Virus [Cullen, et al., *Mol. Cell. Biol.* 5:438-47 (1985)] plus a fragment of the CMV-enhancer [Boshart, et al., *Cell* 41:521-30 (1985)]. Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI, and Asp718, facilitate the
15 cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Example 3(a)

20 Cloning and Expression in COS Cells

The expression plasmid, pLP HA, is made by cloning a cDNA encoding LP polypeptide into the expression vector pCDNAI/Amp or pCDNAIII (which can be obtained from Invitrogen, Inc.).

25 The expression vector pCDNAI/amp contains: (1) an *E. coli* origin of replication effective for propagation in *E. coli* and other prokaryotic cells; (2) an ampicillin resistance gene for selection of plasmid-containing prokaryotic cells; (3) an SV40 origin of replication for
30 propagation in eukaryotic cells; (4) a CMV promoter, a polylinker, an SV40 intron; (5) several codons encoding a hemagglutinin fragment (i.e., an "HA" tag to facilitate

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purification) or HIS tag (see, e.g., Ausubel, *supra*) followed by a termination codon and polyadenylation signal arranged so that a cDNA can be conveniently placed under expression control of the CMV promoter and operably linked to the SV40 intron and the polyadenylation signal by means of restriction sites in the polylinker. The HA tag corresponds to an epitope derived from the influenza hemagglutinin polypeptide described by Wilson, et al., *Cell* 37:767-8 (1984). The fusion of the HA tag to the target polypeptide allows easy detection and recovery of the recombinant polypeptide with an antibody that recognizes the HA epitope. pCDNAIII contains, in addition, the selectable neomycin marker.

A DNA fragment encoding the LP polypeptide is cloned into the polylinker region of the vector so that recombinant polypeptide expression is directed by the CMV promoter. The plasmid construction strategy is as follows. The LP polypeptide-encoding cDNA of a clone is amplified using primers that contain convenient restriction sites, much as described above for construction of vectors for expression of LP polypeptides in *E. coli*. Non-limiting examples of suitable primers include those based on the coding sequences presented in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, and 37.

The PCR amplified DNA fragment and the vector, pCDNAI/Amp, are digested with suitable restriction enzyme(s) and then ligated. The ligation mixture is transformed into *E. coli* strain SURE (available from Stratagene Cloning Systems, La Jolla, CA), and the transformed culture is plated on ampicillin media plates which then are incubated to allow growth of ampicillin resistant colonies. Plasmid DNA is isolated from resistant

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colonies and examined by restriction analysis or other means for the presence of the LP polypeptide-encoding fragment.

For expression of recombinant LP polypeptide, COS
5 cells are transfected with an expression vector, as described above, using DEAE-DEXTRAN, as described, for instance, in Sambrook, et al., *Molecular Cloning: a Laboratory Manual*, Cold Spring Laboratory Press, Cold Spring Harbor, New York (1989). Cells are incubated under
10 conditions for expression of the LP polypeptide-encoding polynucleotide by the vector.

Expression of the LP polypeptide-HA fusion is detected by radiolabeling and immunoprecipitation, using methods described in, for example Harlow, et al., *Antibodies: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1988). To this end,
15 two days after transfection, the cells are labeled by incubation in media containing ³⁵S-cysteine for eight hours. The cells and the media are collected, and the cells are
20 washed and lysed with detergent-containing RIPA buffer: 150 mM sodium chloride, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM TRIS, pH 7.5, as described by Wilson, et al., cited above. Proteins are precipitated from the cell lysate and from the culture media using an HA-specific monoclonal antibody.
25 The precipitated polypeptides then are analyzed by SDS-PAGE and autoradiography. An expression product of the expected size is seen in the cell lysate, which is not seen in negative controls.

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Example 3(b)Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of the LP polypeptide. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary cells or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (alpha minus MEM, Life Technologies) supplemented with methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented [see, e.g., Alt, et al., *J. Biol. Chem.* 253:1357-70 (1978); Hamlin and Ma, *Biochem. et Biophys. Acta* 1097:107-43 (1990); and Page and Sydenham, *Biotechnology* 9:64-8 (1991)]. Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained which contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains for expressing the gene of interest the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus [Cullen, et al., *Mol. Cell. Biol.* 5: 438-47 (1985)] plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) [Boshart, et al., *Cell* 41: 521-30 (1985)].

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Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites, the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human beta-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLVII. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the LP polypeptide in a regulated way in mammalian cells [Gossen, and Bujard, *Proc. Natl. Acad. Sci. USA* 89:5547-51 (1992)]. For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The DNA sequence encoding the complete the LP polypeptide is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene. Non-limiting examples include 5' and 3' primers having nucleotides corresponding or complementary to a portion of the coding sequences of an LP polypeptide-encoding polynucleotide, e.g., as presented in SEQ ID NO:1, 3, 5, 7,

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9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37, according to known method steps.

The amplified fragment is digested with suitable endonucleases and then purified again on a 1% agarose gel.

5 The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

10 Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. Five μg of the expression plasmid pC4 is cotransfected with 0.5 μg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2-neo contains a dominant selectable marker, the neo gene from
15 Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 $\mu\text{g}/\text{mL}$ G418. After two days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM
20 supplemented with 10, 25, or 50 ng/mL of methotrexate plus 1 $\mu\text{g}/\text{mL}$ G418. After about ten to fourteen days, single clones are trypsinized and then seeded in six-well petri dishes or 10 mL flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM).
25 Clones growing at the highest concentrations of methotrexate are then transferred to new six-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a
30 concentration of 100 to 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

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Example 4Tissue Distribution of LP polypeptide-encoding mRNA

Northern blot analysis is carried out to examine
5 expression of LP-polypeptide mRNA in human tissues, using
methods described by, among others, Sambrook, *et al.*, cited
above. A cDNA preferably probe encoding the entire LP
polypeptide is labeled with ^{32}P using the RediprimeTM DNA
labeling system (Amersham Life Science), according to the
10 manufacturer's instructions. After labeling, the probe is
purified using a CHROMA SPIN-100TM column (Clontech
Laboratories, Inc.) according to the manufacturer's protocol
number PT1200-1. The purified and labeled probe is used to
examine various human tissues for LP polypeptide mRNA.
15 Multiple Tissue Northern (MTN) blots containing various
human tissues (H) or human immune system tissues (IM) are
obtained from Clontech and are examined with the labeled
probe using ExpressHybTM hybridization solution (Clontech)
according to manufacturer's protocol number PT1190-1.
20 Following hybridization and washing, the blots are mounted,
exposed to film at negative 70 degrees C overnight, and
developed according to standard procedures.

Example 5Protein Phosphorylation on Tyrosine Residues

25 Protein-induced cell responses are determined by
monitoring tyrosine phosphorylation upon stimulation of
cells by addition of LP polypeptides. This is accomplished
in two steps: cell manipulation and immunodetection.
30 Protein phosphorylation is measured using the SK-N-MC
neuroblastoma cell line (ATCC HTB-10). On day one, the
cells are plated into poly-D-lysine-coated, 96 well plates

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containing cell propagation medium [DMEM:F12 (3:1), 20 mM HEPES at pH 7.5, 5% FBS, and 50 µg/mL Gentamicin]. The cells are seeded at a concentration of 20,000 cells per well in 100 µL medium. On day two, the propagation medium in
5 each well is replaced with 100 µL starvation medium containing DMEM:F12 (3:1), 20 mM HEPES at pH 7.5, 0.5% FBS, and 50 µg/mL Gentamicin. The cells are incubated overnight.

On day three, pervanadate solution is made ten minutes before cell lysis; pervanadate is prepared by mixing 100 µL
10 of sodium orthovanadate (100 mM) and 3.4 µL of hydrogen peroxide (producing 100X stock pervanadate solution). The lysis buffer is then prepared: 50 mM HEPES at pH 7.5, 150 mM sodium chloride, 10% glycerol, 1% TRITON-X100™, 1 mM EDTA, 1 mM pervanadate, and BM protease inhibitors. The
15 cells are stimulated by adding 10 µL of the LP polypeptide solution to the cells, and incubating for ten minutes. Next, the medium is aspirated, and 75 µL lysis buffer are added to each well. The cells are lysed at 4 degrees C for fifteen minutes, then 25 µL of 4X loading buffer are added
20 to the cell lysates. The resultant solution is mixed then heated to 95 degrees C.

Detection of tyrosine phosphorylation is accomplished by Western immunoblotting. Twenty microliters of each cell sample are loaded onto SDS-PAGE eight to sixteen percent
25 amino acid-ready gels from Bio-Rad, and the gels are run. The proteins are electrotransferred in transfer buffer (25 mM Tris base at pH 8.3, 0.2 M glycine, 20% methanol) from the gel to a nitrocellulose membrane using 250 mA per
gel over a one hour period. The membrane is incubated for
30 one hour at ambient conditions in blocking buffer consisting of TBST (20 mM Tris hydrochloride at pH 7.5, 150 mM sodium chloride, 0.1% TWEEN®-20) with 1% BSA.

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Next, the antibodies are added to the membrane. The membrane is incubated overnight at 4 degrees C with gentle rocking in primary antibody solution consisting of the antibody, TBST, and 1% BSA. The next day, the membrane is washed three times, five minutes per wash, with TBST. The membrane is then incubated in the secondary antibody solution consisting of the antibody, TBST, and 1% BSA for one hour at ambient conditions with gentle rocking. After the incubation, the membrane is washed four times with TBST, ten minutes per wash.

Detection is accomplished by incubating the membrane with 10 to 30 mL of SuperSignal Solution for one minute at ambient conditions. After one minute, excess developing solution is removed, and the membrane is wrapped in plastic wrap. The membrane is exposed to X-ray film for twenty second, one minute, and two minute exposures (or longer if needed). The number and intensity of immunostained protein bands are compared to bands for the negative control-stimulated cells (basal level of phosphorylation) by visual comparison.

LP251(a) stimulates phosphorylation in the SK-N-MC cell line and activates the AKT pathway.

Example 6

Cell Stimulation with Detection Utilizing Reporters

Protein-induced cell responses are measured using reporters. The SK-N-MC cell line (neuroblastoma; ATCC HTB-10) / NF κ B reporter combination is used.

For the reporter used, positive controls are designed in the form of agonist cocktails. These cocktails include approximate maximal stimulatory doses of several ligands known to stimulate the regulated signal pathway. For the

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NFkB reporter, the NFkB / PkC pathway is stimulated by an agonist cocktail containing LPS and TNF-alpha as positive controls. Cell lines and reporters with no exogenous stimulus added are used as negative controls.

5 At time zero, the cells are transiently transfected with the reporter plasmids in tissue culture flasks using a standard optimized protocol for all cell lines (see Example 1). After 24 hours, the cells are trypsinized and seeded into 96-well poly-D-lysine coated assay plates at a rate of
10 20,000 cells per well in growth medium. After four to five hours, the medium is replaced with serum-free growth medium. At that time, stimulants for those reporters which required a 24-hour stimulation period are added. After 48 hours, stimulants for the reporters which required a five-hour
15 stimulation period are added. Five hours later, all conditions are lysed using a lysis/luciferin cocktail, and the fluorescence of the samples is determined using a Micro Beta reader.

Each assay plate is plated to contain four positive
20 control wells, sixteen negative control wells, and sixty-four test sample wells (two replicates of thirty-two test samples). The threshold value for a positive "hit" is a fluorescence signal equal to the mean plus two standard deviations of the negative control wells. Any test sample
25 that, in both replicates, generates a signal above that threshold is defined as a "hit."

LP240 stimulates the NFkB pathway of the neuroblastoma cell line SK-N-MC.

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Example 7

Cell Proliferation and Cytotoxicity Determination Utilizing
Fluorescence Detection

This assay is designed to monitor gross changes in the
5 number of cells remaining in culture after exposure to LP
polypeptides for a period of three days. The following
cells are used in this assay:

U373MG (astrocytoma cell line, ATCC HTB-22)
T1165 (plasmacytoma cell line)
10 ECV304 endothelial cell line)

Prior to assay, cells are incubated in an appropriate
assay medium to produce a sub-optimal growth rate, e.g., a
1:10 or 1:20 dilution of normal culture medium. Cells are
15 grown in T-150 flasks, then harvested by trypsin digestion
and replated at 40 to 50% confluence into poly-D-lysine-
treated 96-well plates. Cells are only plated into the
inner thirty-two wells to prevent edge artifacts due to
medium evaporation; the outer wells are filled with buffer
20 alone. Following incubation overnight to stabilize cell
recovery, LP polypeptides are added to the appropriate
wells. Each polypeptide is assayed in triplicate at two
different concentrations, 1X and 0.1X dilution in assay
medium. Two controls are also included on each assay plate:
25 assay medium and normal growth medium.

After approximately 72 hours of exposure, the plates
are processed to determine the number of viable cells.
Plates are spun to increase the attachment of cells to the
plate. The medium is then discarded, and 50 μ L of detection
30 buffer is added to each well. The detection buffer
consisted on MEM medium containing no phenol red (Gibco)
with calcein AM (Molecular Probes) and PLURONIC[®] F-127

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(Molecular Probes), each at a 1:2000 dilution. After incubating the plates in the dark at room temperature for thirty minutes, the fluorescence intensity of each well is measured using a Cytofluor 4000-plate reader (PerSeptive Biosystems). For a given cell type, the larger the fluorescence intensity, the greater the number of cells in the well. To determine the effects on cell growth from each plate, the intensity of each well containing cells stimulated with an LP polypeptide is subtracted from the intensity of the wells containing assay medium only (controls). Thus, a positive number indicated stimulation of cell growth; a negative number indicated a reduction in growth. Additionally, confidence limits at 95 and 90% are calculated from the mean results. Results lying outside the 95% confidence limit are scored as "definite hits." Results lying between the 95 and 90% confidence limits are scored as "maybes." The distinction between definite hits and maybes varied due to intraplate variability; thus, subjective scoring is used as a final determination for "hits."

LP251(a) stimulates the growth of T1165 cells and suppresses the growth of U373MG cells. LP240 stimulates the proliferation of the ECV304 endothelial cell line.

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WE CLAIM:

1. Isolated nucleic acid comprising DNA having at least 90% sequence identity to a polynucleotide selected from the group consisting of:

- (a) a polynucleotide having a nucleotide sequence as shown in SEQ ID NO:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, or 37;
- (b) a polynucleotide encoding a polypeptide having the amino acid sequence as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;
- (c) a polynucleotide encoding the mature form of a polypeptide having the amino acid sequence as shown in SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;
- (d) a polynucleotide fragment of a polynucleotide as in (a), (b), or (c); and
- (e) a polynucleotide having a nucleotide sequence which is complementary to the nucleotide sequence of a polynucleotide as in (a), (b), (c), or (d).

2. An isolated nucleic acid molecule encoding an polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence that encodes LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), LP223(b), or any fragment or variant thereof.

30

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3. The isolated nucleic acid molecule of claim 2, wherein hybridization occurs under stringent hybridization and wash conditions.

5 4. A vector comprising the nucleic acid molecule of any of Claims 1 to 3.

5. The vector of Claim 4, wherein said nucleic acid molecule is operably linked to control sequences recognized by
10 a host cell transformed with the vector.

6. A host cell comprising the vector of Claim 5.

7. A process for producing an LP polypeptide comprising
15 culturing the host cell of Claim 6 under conditions suitable for expression of said LP polypeptide and recovering said LP polypeptide from the cell culture.

8. An isolated polypeptide comprising an amino acid
20 sequence comprising about 90% sequence identity to a sequence of amino acid residues comprising LP105, LP061, LP224, LP240, LP239(a), LP243(a), LP243(b), LP253, LP218, LP251(a), LP252, LP239(b), LP223(a), LP255(a), LP244, LP186, LP251(b), LP255(b), or LP223(b) as shown in SEQ ID NO:2, 4, 6, 8, 10,
25 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38, respectively.

9. An isolated polypeptide comprising a sequence of amino acid residues selected from the group consisting of:
30 (a) SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, or 38;

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- (b) fragments of (a) sufficient to provide a binding site for an LP polypeptide antibody; and
- (c) variants of (a) or (b).

5 10. An isolated polypeptide produced by the method of Claim 7.

11. A chimeric molecule comprising an LP polypeptide fused to a heterologous amino acid sequence.

10

12. The chimeric molecule of Claim 11, wherein said heterologous amino acid sequence is an epitope tag sequence.

13. The chimeric molecule of Claim 12, wherein said
15 heterologous amino acid sequence is an Fc region of an immunoglobulin.

14. An antibody which specifically binds to an LP polypeptide.

20

15. The antibody of Claim 14, where said antibody is a monoclonal antibody.

16. The antibody of Claim 15, wherein said antibody is
25 selected from the group consisting of a humanized antibody and a human antibody.

17. A composition comprising a therapeutically effective amount of an active agent selected from the group consisting
30 of:

- (a) an LP polypeptide;
- (b) an agonist to an LP polypeptide;

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- (c) an antagonist to an LP polypeptide;
- (d) an LP polypeptide antibody;
- (e) an anti-LP polypeptide-encoding mRNA specific ribozyme; and
- 5 (f) a polynucleotide as in Claim 1, in combination with a pharmaceutically acceptable carrier.

18. A method of treating a mammal suffering from a disease, condition, or disorder associated with aberrant
10 levels of an LP-polypeptide comprising administering a therapeutically effective amount of an LP polypeptide or LP polypeptide agonist.

19. A method of diagnosing a disease, condition, or
15 disorder associated with aberrant levels of an LP polypeptide by: (1) culturing test cells or tissues expressing LP polypeptide; (2) administering a compound which can inhibit LP polypeptide modulated signaling; and (3) measuring the LP polypeptide-mediated phenotypic effects in the test cells or
20 tissues.

20. An article of manufacture comprising a container, label and therapeutically effective amount of the composition of Claim 17.

25

21. Use of an LP polypeptide in the manufacture of a medicament for the treatment of a disease, condition, or disorder associated with aberrant levels of an LP polypeptide.

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ttt cat gag agg agt ggc aac tac ctc tgg cac ggc cac ttg aga ctt Phe His Glu Arg Ser Gly Asn Tyr Leu Trp His Gly His Leu Arg Leu 155 160 165 170	638
aaa gaa cac att gac agg aaa ttt gtt ccc ttc caa aag tta cag ttt Lys Glu His Ile Asp Arg Lys Phe Val Pro Phe Gln Lys Leu Gln Phe 175 180 185	686
ggg cgt tat cca gga gct ttt gac agg cca gag tta cag caa gtt act Gly Arg Tyr Pro Gly Ala Phe Asp Arg Pro Glu Leu Gln Gln Val Thr 190 195 200	734
gtt gat gga ctg gaa gtt ctc att cca aag gat cca atg cac ttt gta Val Asp Gly Leu Glu Val Leu Ile Pro Lys Asp Pro Met His Phe Val 205 210 215	782
gaa gaa gta cca cac tct agg ttt att gag tgt agg tat aaa gaa gct Glu Glu Val Pro His Ser Arg Phe Ile Glu Cys Arg Tyr Lys Glu Ala 220 225 230	830

cga gca ttc ttt cag ata cct gtt tcc gaa gtt tac act gtg ctg gac 878
 Arg Ala Phe Phe Gln Ile Pro Val Ser Glu Val Tyr Thr Val Leu Asp
 235 240 245 250

tgagtttgta gacatgaagg tccatgtacc ctgtgaaacc ctcgaataca ttgaagccaa 938

ctatggtaag acctggaaga ttctgtataa gacgtgggac tggaagcgct ctcctcccaa 998

tgtgcaaccc aatggaatct ggcctatttc tgagtgggat gag 1041

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<211> 271

<212> PRT

<213> Homo sapiens

<400> 4

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 -5 -1 1 5 10

Ser Thr Lys Asn Gly Ala Gly Leu Ser Lys Ser Lys Gly Ser Arg Ile
 15 20 25

Gly Phe Asp Ser Thr Gln Trp Arg Ala Val Lys Lys Phe Ile Met Leu
 30 35 40

Thr Ser Asn Gln Asn Val Pro Val Phe Leu Ile Asp Pro Leu Ile Leu
 45 50 55

Glu Leu Ile Asn Lys Asn Phe Glu Gln Val Lys Asn Thr Ser His Gly
 60 65 70 75

Ser Thr Ser Gln Cys Lys Phe Phe Cys Val Pro Arg Asp Phe Thr Ala
 80 85 90

Phe Ala Leu Gln Tyr His Leu Trp Lys Asn Glu Glu Gly Trp Phe Arg
 95 100 105

Ile Ala Glu Asn Met Gly Phe Gln Cys Leu Lys Ile Glu Ser Lys Asp
 110 115 120

Pro Arg Leu Asp Gly Ile Asp Ser Leu Ser Gly Thr Glu Ile Pro Leu
125 130 135

His Tyr Ile Cys Lys Leu Ala Thr His Ala Ile His Leu Val Val Phe
140 145 150 155

His Glu Arg Ser Gly Asn Tyr Leu Trp His Gly His Leu Arg Leu Lys
160 165 170

Glu His Ile Asp Arg Lys Phe Val Pro Phe Gln Lys Leu Gln Phe Gly
175 180 185

Arg Tyr Pro Gly Ala Phe Asp Arg Pro Glu Leu Gln Gln Val Thr Val
190 195 200

Asp Gly Leu Glu Val Leu Ile Pro Lys Asp Pro Met His Phe Val Glu
205 210 215

Glu Val Pro His Ser Arg Phe Ile Glu Cys Arg Tyr Lys Glu Ala Arg
220 225 230 235

Ala Phe Phe Gln Ile Pro Val Ser Glu Val Tyr Thr Val Leu Asp
240 245 250

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<220>
<221> mutation
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<223> variant wherein nucleotides 383-385 are deleted

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<222> (416)..()

<220>

<221> sig_peptide

<222> (1)..(23)

<223> wherein Leu at position -11 may be deleted

<400> 5

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ggcgggccgcc cagcagccccg ggctcgggtg ggggggcgcc gagtgggggt ggcggccagc 180

atgctgctcg gctgcggctc ggctccccc acccgcgggt ccctagtcct cgccagcagc 240

ggcgggcgga gagcagcgag cggcgccccg gtctgcagcg gcgccgggtc cgagcgcgcg 300

gcgcggcggt gggggtcggg gcccgggcg ggagcgggga ccgggc atg gcg ctg 355
Met Ala Leucgg aga ggc ggc tgc gga gcg ctc ggg ctg ctg ctg ctg ctg ctg ggc 403
Arg Arg Gly Gly Cys Gly Ala Leu Gly Leu Leu Leu Leu Leu Leu Gly
-20 -15 -10 -5gcc gcg tgc ctg ata ccg cgg agc gcg cag gtg agg cgg ctg gcg cgc 451
Ala Ala Cys Leu Ile Pro Arg Ser Ala Gln Val Arg Arg Leu Ala Arg
-1 1 5 10tgc ccc gcc act tgc agc tgt acc aag gag tct atc atc tgc gtg ggc 499
Cys Pro Ala Thr Cys Ser Cys Thr Lys Glu Ser Ile Ile Cys Val Gly
15 20 25tct tcc tgg gtg ccc agg atc gtg ccg ggc gac atc agc tcc ctg agc 547
Ser Ser Trp Val Pro Arg Ile Val Pro Gly Asp Ile Ser Ser Leu Ser
30 35 40ctg gta aat ggg acg ttt tca gaa atc aag gac cga atg ttt tcc cat 595
Leu Val Asn Gly Thr Phe Ser Glu Ile Lys Asp Arg Met Phe Ser His
45 50 55 60ctg cct tct ctg cag ctg cta ttg ctg aat tct aac tca ttc acg atc 643
Leu Pro Ser Leu Gln Leu Leu Leu Leu Asn Ser Asn Ser Phe Thr Ile
65 70 75atc cgg gat gat gct ttt gct gga ctt ttt cat ctt gaa tac ctg ttc 691
Ile Arg Asp Asp Ala Phe Ala Gly Leu Phe His Leu Glu Tyr Leu Phe
80 85 90att gaa ggg aac aaa ata gaa acc att tca aga aat gcc ttt cgt ggc 739
Ile Glu Gly Asn Lys Ile Glu Thr Ile Ser Arg Asn Ala Phe Arg Gly
95 100 105

ctc cgt gac ctg act cac ctt tct ttg gcc aat aac cac ata aaa gca	787
Leu Arg Asp Leu Thr His Leu Ser Leu Ala Asn Asn His Ile Lys Ala	
110 115 120	
cta cca agg gat gtc ttc agt gat tta gac tct ctg att gaa cta gat	835
Leu Pro Arg Asp Val Phe Ser Asp Leu Asp Ser Leu Ile Glu Leu Asp	
125 130 135 140	
ttg agg ggt aat aaa ttt gaa tgt gac tgc aaa gcc aag tgg cta tac	883
Leu Arg Gly Asn Lys Phe Glu Cys Asp Cys Lys Ala Lys Trp Leu Tyr	
145 150 155	
ctg tgg ttg aag atg aca aat tcc acc gtt tct gat gtg ctg tgt att	931
Leu Trp Leu Lys Met Thr Asn Ser Thr Val Ser Asp Val Leu Cys Ile	
160 165 170	
ggt cca cca gag tat cag gaa aag aag cta aat gac gtg acc agc ttt	979
Gly Pro Pro Glu Tyr Gln Glu Lys Lys Leu Asn Asp Val Thr Ser Phe	
175 180 185	
gac tat gaa tgc aca act aca gat ttt gtt gtt cat cag act tta ccc	1027
Asp Tyr Glu Cys Thr Thr Thr Asp Phe Val Val His Gln Thr Leu Pro	
190 195 200	
tac cag tcg gtt tca gtg gat acg ttc aac tcc aag aac gat gtg tac	1075
Tyr Gln Ser Val Ser Val Asp Thr Phe Asn Ser Lys Asn Asp Val Tyr	
205 210 215 220	
gtg gcc atc gcg cag ccc agc atg gag aac tgc atg gtg ctg gag tgg	1123
Val Ala Ile Ala Gln Pro Ser Met Glu Asn Cys Met Val Leu Glu Trp	
225 230 235	
gac cac att gaa atg aat ttc cgg agc tat gac aac att aca ggt cag	1171
Asp His Ile Glu Met Asn Phe Arg Ser Tyr Asp Asn Ile Thr Gly Gln	
240 245 250	
tcc atc gtg ggc tgt aag gcc att ctc atc gat gat cag gtc ttt gtg	1219
Ser Ile Val Gly Cys Lys Ala Ile Leu Ile Asp Asp Gln Val Phe Val	
255 260 265	
gtg gta gcc cag ctc ttc ggt ggc tct cac att tac aaa tac gac gag	1267
Val Val Ala Gln Leu Phe Gly Gly Ser His Ile Tyr Lys Tyr Asp Glu	
270 275 280	
agt tgg acc aaa ttt gtc aaa ttc caa gac ata gag gtc tct cgc att	1315
Ser Trp Thr Lys Phe Val Lys Phe Gln Asp Ile Glu Val Ser Arg Ile	
285 290 295 300	
tcc aag ccc aat gac atc gag ctg ttt cag atc gac gac gag acg ttc	1363
Ser Lys Pro Asn Asp Ile Glu Leu Phe Gln Ile Asp Asp Glu Thr Phe	
305 310 315	

ttt gtc atc gca gac agc tca aag gct ggt ctg tcc aca gtt tat aaa	1411
Phe Val Ile Ala Asp Ser Ser Lys Ala Gly Leu Ser Thr Val Tyr Lys	
320 325 330	
tggt aac agc aaa gga ttc tat tct tac cag tca ctg cac gag tgg ttc	1459
Trp Asn Ser Lys Gly Phe Tyr Ser Tyr Gln Ser Leu His Glu Trp Phe	
335 340 345	
agg gac acg gat gcg gag ttt gtt gat atc gat gga aaa tcg cat ctc	1507
Arg Asp Thr Asp Ala Glu Phe Val Asp Ile Asp Gly Lys Ser His Leu	
350 355 360	
atc ctg tcc agc cgc tcc cag gtc ccc atc atc ctc cag tgg aat aaa	1555
Ile Leu Ser Ser Arg Ser Gln Val Pro Ile Ile Leu Gln Trp Asn Lys	
365 370 375 380	
agc tct aag aag ttt gtc ccc cat ggt gac atc ccc aac atg gag gac	1603
Ser Ser Lys Lys Phe Val Pro His Gly Asp Ile Pro Asn Met Glu Asp	
385 390 395	
gta ctg gct gtg aag agc ttc cga atg caa aat acc ctc tac ctt tcc	1651
Val Leu Ala Val Lys Ser Phe Arg Met Gln Asn Thr Leu Tyr Leu Ser	
400 405 410	
ctt acc cgc ttc atc ggg gac tcc cgg gtc atg agg tgg aac agt aag	1699
Leu Thr Arg Phe Ile Gly Asp Ser Arg Val Met Arg Trp Asn Ser Lys	
415 420 425	
cag ttt gtg gag atc caa gct ctt cca tcc cgg ggg gcc atg acc ctg	1747
Gln Phe Val Glu Ile Gln Ala Leu Pro Ser Arg Gly Ala Met Thr Leu	
430 435 440	
cag ccc ttt tct ttt aaa gat aat cac tac ctg gcc ctg ggg agt gac	1795
Gln Pro Phe Ser Phe Lys Asp Asn His Tyr Leu Ala Leu Gly Ser Asp	
445 450 455 460	
tat aca ttc tct cag ata tac cag tgg gat aaa gag aag cag cta ttc	1843
Tyr Thr Phe Ser Gln Ile Tyr Gln Trp Asp Lys Glu Lys Gln Leu Phe	
465 470 475	
aaa aag ttt aag gag att tac gtg cag gcg cct cgt tca ttc aca gct	1891
Lys Lys Phe Lys Glu Ile Tyr Val Gln Ala Pro Arg Ser Phe Thr Ala	
480 485 490	
gtc tcc acc gac agg aga gat ttc ttt ttt gca tcc agt ttc aaa ggg	1939
Val Ser Thr Asp Arg Arg Asp Phe Phe Phe Ala Ser Ser Phe Lys Gly	
495 500 505	
aaa aca aag att ttt gaa cat ata att gtt gac tta agt ttg	1981
Lys Thr Lys Ile Phe Glu His Ile Ile Val Asp Leu Ser Leu	
510 515 520	
tgaaggtgtg gtgggtgaaa ctaagagaaa tgtagcatta gctctcacia aagaggacca	2041

agaaaaatca acaaacaaat caaagccagg ctgagagctc tgaaattaaa aagcactgaa	2101
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ctaactgcat gacatgccca ttctaccatt ttaaaaaaaaa tcttaaagcc tgtaatttct	2221
gagaaaagag tacagcattt actcttatca tctagaaatg taatatgctt ccccccgct	2281
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cggtagaatt tttgaagtga gattttatga agtcaaagg gactttacac agatctcgac	2941
ctgctttgaa acctagaggt ggccctttga tttgtgctg tccttgcct ctggacaact	3001
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tgtgtaacag tcctgttttg ttgagttgct gctattgcac tgccagtga gccacacca	3121
aatcacaacc caagatactc agataggaag actccttcct ctcccagtac tttaccaaa	3181
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gcaataggca agctcctggg gtctgggtat gtggaagatt cttagtggat gttccgcctg	3421
gtagctgggt tctcttcaga gaatataaag tgaatgcctt taggggtagc tctgaaagag	3481
aaaccaaca acttcattcc tagccatgaa agtagcacga tcatattgta ctgtattgtt	3541
attgtaaaat gactatttgc catgtcatga gtaggtagat gttttgccac aaatatgaat	3601

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atg 3664

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<211> 545

<212> PRT

<213> Homo sapiens

<400> 6

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-5 -1 1 5

Leu Ala Arg Cys Pro Ala Thr Cys Ser Cys Thr Lys Glu Ser Ile Ile
10 15 20 25

Cys Val Gly Ser Ser Trp Val Pro Arg Ile Val Pro Gly Asp Ile Ser
30 35 40

Ser Leu Ser Leu Val Asn Gly Thr Phe Ser Glu Ile Lys Asp Arg Met
45 50 55

Phe Ser His Leu Pro Ser Leu Gln Leu Leu Leu Leu Asn Ser Asn Ser
60 65 70

Phe Thr Ile Ile Arg Asp Asp Ala Phe Ala Gly Leu Phe His Leu Glu
75 80 85

Tyr Leu Phe Ile Glu Gly Asn Lys Ile Glu Thr Ile Ser Arg Asn Ala
90 95 100 105

Phe Arg Gly Leu Arg Asp Leu Thr His Leu Ser Leu Ala Asn Asn His
110 115 120

Ile Lys Ala Leu Pro Arg Asp Val Phe Ser Asp Leu Asp Ser Leu Ile
125 130 135

Glu Leu Asp Leu Arg Gly Asn Lys Phe Glu Cys Asp Cys Lys Ala Lys
140 145 150

Trp Leu Tyr Leu Trp Leu Lys Met Thr Asn Ser Thr Val Ser Asp Val
 155 160 165

Leu Cys Ile Gly Pro Pro Glu Tyr Gln Glu Lys Lys Leu Asn Asp Val
 170 175 180 185

Thr Ser Phe Asp Tyr Glu Cys Thr Thr Thr Asp Phe Val Val His Gln
 190 195 200

Thr Leu Pro Tyr Gln Ser Val Ser Val Asp Thr Phe Asn Ser Lys Asn
 205 210 215

Asp Val Tyr Val Ala Ile Ala Gln Pro Ser Met Glu Asn Cys Met Val
 220 225 230

Leu Glu Trp Asp His Ile Glu Met Asn Phe Arg Ser Tyr Asp Asn Ile
 235 240 245

Thr Gly Gln Ser Ile Val Gly Cys Lys Ala Ile Leu Ile Asp Asp Gln
 250 255 260 265

Val Phe Val Val Val Ala Gln Leu Phe Gly Gly Ser His Ile Tyr Lys
 270 275 280

Tyr Asp Glu Ser Trp Thr Lys Phe Val Lys Phe Gln Asp Ile Glu Val
 285 290 295

Ser Arg Ile Ser Lys Pro Asn Asp Ile Glu Leu Phe Gln Ile Asp Asp
 300 305 310

Glu Thr Phe Phe Val Ile Ala Asp Ser Ser Lys Ala Gly Leu Ser Thr
 315 320 325

Val Tyr Lys Trp Asn Ser Lys Gly Phe Tyr Ser Tyr Gln Ser Leu His
 330 335 340 345

Glu Trp Phe Arg Asp Thr Asp Ala Glu Phe Val Asp Ile Asp Gly Lys
 350 355 360

Ser His Leu Ile Leu Ser Ser Arg Ser Gln Val Pro Ile Ile Leu Gln
 365 370 375

Trp Asn Lys Ser Ser Lys Lys Phe Val Pro His Gly Asp Ile Pro Asn
 380 385 390

Met Glu Asp Val Leu Ala Val Lys Ser Phe Arg Met Gln Asn Thr Leu
 395 400 405

Tyr Leu Ser Leu Thr Arg Phe Ile Gly Asp Ser Arg Val Met Arg Trp
 410 415 420 425

Asn Ser Lys Gln Phe Val Glu Ile Gln Ala Leu Pro Ser Arg Gly Ala
 430 435 440

Met Thr Leu Gln Pro Phe Ser Phe Lys Asp Asn His Tyr Leu Ala Leu
 445 450 455

Gly Ser Asp Tyr Thr Phe Ser Gln Ile Tyr Gln Trp Asp Lys Glu Lys
 460 465 470

Gln Leu Phe Lys Lys Phe Lys Glu Ile Tyr Val Gln Ala Pro Arg Ser
 475 480 485

Phe Thr Ala Val Ser Thr Asp Arg Arg Asp Phe Phe Phe Ala Ser Ser
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Phe Lys Gly Lys Thr Lys Ile Phe Glu His Ile Ile Val Asp Leu Ser
 510 515 520

Leu

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gcg gcg ctg gcc cac ggc tgt ctg cac tgc cac agc aac ttc tcc aag	99		
Ala Ala Leu Ala His Gly Cys Leu His Cys His Ser Asn Phe Ser Lys			
		-1 1 5 10	
aag ttc tcc ttc tac cgc cac cat gtg aac ttc aag tcc tgg tgg gtg	147		
Lys Phe Ser Phe Tyr Arg His His Val Asn Phe Lys Ser Trp Trp Val			
		15 20 25	
ggc gac atc ccc gtg tca ggg gcg ctg ctc acc gac tgg agc gac gac	195		
Gly Asp Ile Pro Val Ser Gly Ala Leu Leu Thr Asp Trp Ser Asp Asp			
		30 35 40	
acg atg aag gag ctg cac ctg gcc atc ccc gcc aag atc acc cgg gag	243		
Thr Met Lys Glu Leu His Leu Ala Ile Pro Ala Lys Ile Thr Arg Glu			
		45 50 55 60	
aag ctg gac caa gtg gcg aca gca gtg tac cag atg atg gat cag ctg	291		
Lys Leu Asp Gln Val Ala Thr Ala Val Tyr Gln Met Met Asp Gln Leu			
		65 70 75	
tac cag ggg aag atg tac ttc ccc ggg tat ttc ccc aac gag ctg cga	339		
Tyr Gln Gly Lys Met Tyr Phe Pro Gly Tyr Phe Pro Asn Glu Leu Arg			
		80 85 90	
aac atc ttc cgg gag cag gtg cac ctc atc cag aac gcc atc atc gaa	387		
Asn Ile Phe Arg Glu Gln Val His Leu Ile Gln Asn Ala Ile Ile Glu			
		95 100 105	
agc cgc atc gac tgt cag cac cgc tgt ggc atc ttc cag tac gag acc	435		
Ser Arg Ile Asp Cys Gln His Arg Cys Gly Ile Phe Gln Tyr Glu Thr			
		110 115 120	
atc tcc tgc aac aac tgc aca gac tcg cac gtc gcc tgc ttt ggc tat	483		
Ile Ser Cys Asn Asn Cys Thr Asp Ser His Val Ala Cys Phe Gly Tyr			
		125 130 135 140	
aac tgc gag tcc tcg gcg cag tgg aag tca gct gtc cag ggc ctc ctg	531		
Asn Cys Glu Ser Ser Ala Gln Trp Lys Ser Ala Val Gln Gly Leu Leu			
		145 150 155	
aac tac ata aat aac tgg cac aac ctg gta tcg cca gcc tta agg tgt	579		
Asn Tyr Ile Asn Asn Trp His Asn Leu Val Ser Pro Ala Leu Arg Cys			
		160 165 170	

ctg gag ccc cca cac ttg gcc aac ctg acc ttg gaa aat gct gct gag 627
 Leu Glu Pro Pro His Leu Ala Asn Leu Thr Leu Glu Asn Ala Ala Glu
 175 180 185
 tgt ctc aag cag cac tgacagcagc tgggcctgcc ccagggcaac gtgggggcgg 682
 Cys Leu Lys Gln His
 190
 agactcagct ggacagcccc tgctgtcac tctggagctg ggctgctgct gcctcaggac 742
 cccctctccg accccggaca gagctgagct ggccagggcc aggagggcgg gagggaggga 802
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<400> 8

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 5 10 15

Arg His His Val Asn Phe Lys Ser Trp Trp Val Gly Asp Ile Pro Val
 20 25 30

Ser Gly Ala Leu Leu Thr Asp Trp Ser Asp Asp Thr Met Lys Glu Leu
 35 40 45

His Leu Ala Ile Pro Ala Lys Ile Thr Arg Glu Lys Leu Asp Gln Val
 50 55 60 65

Ala Thr Ala Val Tyr Gln Met Met Asp Gln Leu Tyr Gln Gly Lys Met
 70 75 80

Tyr Phe Pro Gly Tyr Phe Pro Asn Glu Leu Arg Asn Ile Phe Arg Glu
 85 90 95

Gln Val His Leu Ile Gln Asn Ala Ile Ile Glu Ser Arg Ile Asp Cys
 100 105 110

Gln His Arg Cys Gly Ile Phe Gln Tyr Glu Thr Ile Ser Cys Asn Asn
 115 120 125

Cys Thr Asp Ser His Val Ala Cys Phe Gly Tyr Asn Cys Glu Ser Ser
 130 135 140 145

Ala Gln Trp Lys Ser Ala Val Gln Gly Leu Leu Asn Tyr Ile Asn Asn
 150 155 160

Trp His Asn Leu Val Ser Pro Ala Leu Arg Cys Leu Glu Pro Pro His
 165 170 175

Leu Ala Asn Leu Thr Leu Glu Asn Ala Ala Glu Cys Leu Lys Gln His
 180 185 190

<210> 9
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 atattttggtt ccaaa atg gca tct tac ctt tat gga gta ctc ttt gct gtt 171
 Met Ala Ser Tyr Leu Tyr Gly Val Leu Phe Ala Val
 -20 -15 -10
 ggc ctc tgt gct cca atc tac tgt gtg tcc ccg gcc aat gcc ccc agt 219
 Gly Leu Cys Ala Pro Ile Tyr Cys Val Ser Pro Ala Asn Ala Pro Ser
 -5 -1 1 5
 gca tac ccc cgc cct tcc tcc aca aag agc acc cct gcc tca cag gtg 267
 Ala Tyr Pro Arg Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val
 10 15 20

tat tcc ctc aac acc gac ttt gcc ttc cgc cta tac cgc agg ctg gtt	315
Tyr Ser Leu Asn Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val	
25 30 35 40	
ttg gag acc ccg agt cag aac atc ttc ttc tcc cct gtg agt gtc tcc	363
Leu Glu Thr Pro Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser	
45 50 55	
act tcc ctg gcc atg ctc tcc ctt ggg gcc cac tca gtc acc aag acc	411
Thr Ser Leu Ala Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr	
60 65 70	
cag att ctc cag ggc ctg ggc ttc aac ctc aca cac aca cca gag tct	459
Gln Ile Leu Gln Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser	
75 80 85	
gcc atc cac cag ggc ttc cag cac ctg gtt cac tca ctg act gtt ccc	507
Ala Ile His Gln Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro	
90 95 100	
agc aaa gac ctg acc ttg aag atg gga agt gcc ctc ttc gtc aag aag	555
Ser Lys Asp Leu Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys	
105 110 115 120	
gag ctg cag ctg cag gca aat ttc ttg ggc aat gtc aag agg ctg tat	603
Glu Leu Gln Leu Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr	
125 130 135	
gaa gca gaa gtc ttt tct aca gat ttc tcc aac ccc tcc att gcc cag	651
Glu Ala Glu Val Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln	
140 145 150	
gcg agg atc aac agc cat gtg aaa aag aag acc caa ggg aag gtt gta	699
Ala Arg Ile Asn Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val	
155 160 165	
gac ata atc caa ggc ctt gac ctt ctg acg gcc atg gtt ctg gtg aac	747
Asp Ile Ile Gln Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn	
170 175 180	
cac att ttc ttt aaa gcc aag tgg gag aag ccc ttt cac cct gaa tat	795
His Ile Phe Phe Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr	
185 190 195 200	
aca aga aag aac ttc cca ttc ctg gtg ggc gag cag gtc act gtg cat	843
Thr Arg Lys Asn Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His	
205 210 215	
gtc ccc atg atg cac cag aaa gag cag ttc gct ttt ggg gtg gat aca	891
Val Pro Met Met His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr	
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gcc ttc ttt gtc ctc cct agc aag ggc aag atg agg caa ctg gaa cag Ala Phe Phe Val Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln 250 255 260	987
gcc ttg tca gcc aga aca ctg aga aag tgg agc cac tca ctc cag aaa Ala Leu Ser Ala Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys 265 270 275 280	1035
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aat ctg gaa acc atc ctc ccg aag atg ggc atc caa aat gtc ttt gac Asn Leu Glu Thr Ile Leu Pro Lys Met Gly Ile Gln Asn Val Phe Asp 300 305 310	1131
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tct aaa gca acc cac aag gct gtg ctg gat gtc agt gaa gag ggc act Ser Lys Ala Thr His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr 330 335 340	1227
gag gcc aca gca gct acc acc acc aag ttc ata gtc cga tcg aag gat Glu Ala Thr Ala Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp 345 350 355 360	1275
ggc ccc tct tac ttc act gtc tcc ttc aat agg acc ttc ctg atg atg Gly Pro Ser Tyr Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met 365 370 375	1323
att aca aat aaa gcc aca gac ggt att ctc ttt cta ggg aaa gtg gaa Ile Thr Asn Lys Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu 380 385 390	1371
aat ccc act aaa tcc taggtgggaa atggcctgtt aactgatggc acattgctaa Asn Pro Thr Lys Ser 395	1426
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Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
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Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
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Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
 45 50 55 60

Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
 65 70 75

Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
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Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
 95 100 105

Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
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Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
 125 130 135 140

Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
 145 150 155

Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
 160 165 170

Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
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Lys Ala Lys Trp Glu Lys Pro Phe His Pro Glu Tyr Thr Arg Lys Asn
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Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val His Val Pro Met Met
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His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
 225 230 235

Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
 240 245 250

Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
 255 260 265

Arg Thr Leu Arg Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
 270 275 280

Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
 285 290 295 300

Ile Leu Pro Lys Met Gly Ile Gln Asn Val Phe Asp Lys Asn Ala Asp
 305 310 315

Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
 320 325 330

His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
 335 340 345

Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
 350 355 360

Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
 365 370 375 380

acg ctg ctg gac ctg agc gag aac aag ctg gta atc ctg ctg gac tac	338
Thr Leu Leu Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr	
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act ttc cag gac ctg cac agc ctg cgc cgg ctg gaa gtg ggc gac aac	386
Thr Phe Gln Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn	
85 90 95	
gac ctg gta ttc gtc tcg cgc cgc gcc ttc gcg ggg ctg ctg gcc ctg	434
Asp Leu Val Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu	
100 105 110	
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Glu Glu Leu Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu	
115 120 125	
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Ser Leu Gly His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu	
130 135 140 145	
gcc atc gcc tcc ctg gag gac cag aac ttc cgc agg ctg ccc ggg ctg	578
Ala Ile Ala Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu	
150 155 160	
ctg cac ctg gag att gac aac tgg ccg ctg ctg gag gag gtg gcg gcg	626
Leu His Leu Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala	
165 170 175	
ggc agc ctg cgc ggc ctg aac ctg acc tcg ctg tcg gtc acc cac acc	674
Gly Ser Leu Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr	
180 185 190	
aac atc acc gcc gtg ccg gcc gcc gcg ctg cgc cac cag gcg cac ctc	722
Asn Ile Thr Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu	
195 200 205	
acc tgc ctc aat ctg tcg cac aac ccc atc agc acg gtg ccg cgc ggg	770
Thr Cys Leu Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly	
210 215 220 225	
tcg ttc cgc gac ctg gtc cgc ctg cgc gag ctg cac ctg gcc ggc gcc	818
Ser Phe Arg Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala	
230 235 240	
ctg ctg gct gtg gtg gag ccg cag gcc ttc ctg ggc ctg cgc cag atc	866
Leu Leu Ala Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile	
245 250 255	
cgc ctg ctc aac ctc tcc aac aac ctg ctc tcc acg ttg gag gag agc	914
Arg Leu Leu Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser	
260 265 270	

acc ttc cac tcg gtg aac acg cta gag acg ctg cgc gtg gac ggg aac	962
Thr Phe His Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn	
275 280 285	
ccg ctg gcc tgc gac tgt cgc ctg ctg tgg atc gtg cag cgt cgc aag	1010
Pro Leu Ala Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys	
290 295 300 305	
acc ctc aac ttc gac ggg cgg ctg ccg gcc tgc gcc acc ccg gcc gag	1058
Thr Leu Asn Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu	
310 315 320	
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Val Arg Gly Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu	
325 330 335	
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Tyr Phe Val Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg	
340 345 350	
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Val Thr Ala Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu	
355 360 365	
ggc gag ccg gcg ccc acc gtg gcc tgg gtg acc ccc cag cac cgg ccg	1250
Gly Glu Pro Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro	
370 375 380 385	
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Val Thr Ala Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr	
390 395 400	
ctg gag atc cag gac gcg cgg ccg cag gac agc ggc acc tac acg tgc	1346
Leu Glu Ile Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys	
405 410 415	
gtg gcc agc aac gcg ggc ggc aac gac acc tac ttc gcc acg ctg acc	1394
Val Ala Ser Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr	
420 425 430	
gtg cgc ccc gag ccg gcc gcc aac cgg acc ccg ggc gag gcc cac aac	1442
Val Arg Pro Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn	
435 440 445	
gag acg ctg gcg gcc ctg cgc gcg ccg ctc gac ctc acc acc atc ctg	1490
Glu Thr Leu Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu	
450 455 460 465	
gtg tcc acc gcc atg ggc tgc atc acc ttc ctg ggc gtg gtc ctc ttc	1538
Val Ser Thr Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe	
470 475 480	

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 Cys Phe Val Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys
 485 490 495
 aac aac ttc tcg gtg gag tac tcc ttc cgc aag gtg gat ggg ccg gcc 1634
 Asn Asn Phe Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala
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 gcc gcg gcg ggc cag gga ggc gcg cgc aag ttc aac atg aag atg atc 1682
 Ala Ala Ala Gly Gln Gly Gly Ala Arg Lys Phe Asn Met Lys Met Ile
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 tgaggggtcc ccagggcgga ccctcccctc ccctcccccg cgggccgggc gctcgcgtgt 1742
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Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly Ala Phe Ala
 25 30 35

Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn Gln Leu Lys
 40 45 50

Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu Thr Leu Leu
 55 60 65

Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr Thr Phe Gln
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Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn Asp Leu Val
 85 90 95 100

Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu Glu Glu Leu
 105 110 115

Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu Ser Leu Gly
 120 125 130

His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu Ala Ile Ala
 135 140 145

Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu Leu His Leu
 150 155 160

Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala Gly Ser Leu
 165 170 175 180

Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr Asn Ile Thr
 185 190 195

Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu Thr Cys Leu
 200 205 210

Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly Ser Phe Arg
 215 220 225

Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala Leu Leu Ala
 230 235 240

Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile Arg Leu Leu
 245 250 255 260

Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser Thr Phe His
 265 270 275

Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn Pro Leu Ala
 280 285 290

Cys Asp Cys Arg Leu Leu Trp Ile Val Gln Arg Arg Lys Thr Leu Asn
 295 300 305

Phe Asp Gly Arg Leu Pro Ala Cys Ala Thr Pro Ala Glu Val Arg Gly
 310 315 320

Asp Ala Leu Arg Asn Leu Pro Asp Ser Val Leu Phe Glu Tyr Phe Val
 325 330 335 340

Cys Arg Lys Pro Lys Ile Arg Glu Arg Arg Leu Gln Arg Val Thr Ala
 345 350 355

Thr Ala Gly Glu Asp Val Arg Phe Leu Cys Arg Ala Glu Gly Glu Pro
 360 365 370

Ala Pro Thr Val Ala Trp Val Thr Pro Gln His Arg Pro Val Thr Ala
 375 380 385

Thr Ser Ala Gly Arg Ala Arg Val Leu Pro Gly Gly Thr Leu Glu Ile
 390 395 400

Gln Asp Ala Arg Pro Gln Asp Ser Gly Thr Tyr Thr Cys Val Ala Ser
 405 410 415 420

Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr Val Arg Pro
 425 430 435

Glu Pro Ala Ala Asn Arg Thr Pro Gly Glu Ala His Asn Glu Thr Leu
 440 445 450

Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu Val Ser Thr
 455 460 465

Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe Cys Phe Val
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Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys Asn Asn Phe
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Trp Leu Cys Val Leu Ser Leu Pro Leu Leu Leu Leu Pro Ala Ala Pro
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Ile Pro Ala Glu Thr Arg Leu Leu Glu Leu Ser Arg Asn Arg Ile Arg
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tgc ctg aac ccg ggc gac ctg gcc gcg ctg ccc gcg ctg gag gag ctg 297
Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu Glu Glu Leu
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gac ctg agc gag aac gcc atc gcg cac gtg gag ccc ggc gcc ttc gcc 345
Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly Ala Phe Ala
60 65 70 75

aac ctg ccg cgc ctg cgc gtc ctg cgt ctc cgt ggc aac cag ctg aag	393
Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn Gln Leu Lys	
80 85 90	
ctc atc ccg ccc ggg gtc ttc acg cgc ctg gac aac ctc acg ctg ctg	441
Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu Thr Leu Leu	
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Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr Thr Phe Gln	
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Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn Asp Leu Val	
125 130 135	
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Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu Glu Glu Leu	
140 145 150 155	
acc ctg gag cgc tgc aac ctc acg gct ctg tcc ggg gag tcg ctg ggc	633
Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu Ser Leu Gly	
160 165 170	
cat ctg cgc agc ctg ggc gcc ctg cgg ctg cgc cac ctg gcc atc gcc	681
His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu Ala Ile Ala	
175 180 185	
tcc ctg gag gac cag aac ttc cgc agg ctg ccc ggg ctg ctg cac ctg	729
Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu Leu His Leu	
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gag att gac aac tgg ccg ctg ctg gag gag gtg gcg gcg ggc agc ctg	777
Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala Gly Ser Leu	
205 210 215	
cgg ggc ctg aac ctg acc tcg ctg tcg gtc acc cac acc aac atc acc	825
Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr Asn Ile Thr	
220 225 230 235	
gcc gtg ccg gcc gcc gcg ctg cgg cac cag gcg cac ctc acc tgc ctc	873
Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu Thr Cys Leu	
240 245 250	
aat ctg tcg cac aac ccc atc agc acg gtg ccg cgg ggg tcg ttc cgg	921
Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly Ser Phe Arg	
255 260 265	
gac ctg gtc cgc ctg cgc gag ctg cac ctg gcc ggg gcc ctg ctg gct	969
Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala Leu Leu Ala	
270 275 280	

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aac gcg ggc ggc aac gac acc tac ttc gcc acg ctg acc gtg cgc ccc Asn Ala Gly Gly Asn Asp Thr Tyr Phe Ala Thr Leu Thr Val Arg Pro 460 465 470 475	1545
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gcg gcc ctg cgc gcg ccg ctc gac ctc acc acc atc ctg gtg tcc acc 1641
Ala Ala Leu Arg Ala Pro Leu Asp Leu Thr Thr Ile Leu Val Ser Thr
495 500 505

gcc atg ggc tgc atc acc ttc ctg ggc gtg gtc ctc ttc tgc ttc gtg 1689
Ala Met Gly Cys Ile Thr Phe Leu Gly Val Val Leu Phe Cys Phe Val
510 515 520

ctg ctg ttc gtg tgg agc cgc ggc cgc ggg cag cac aaa aac aac ttc 1737
Leu Leu Phe Val Trp Ser Arg Gly Arg Gly Gln His Lys Asn Asn Phe
525 530 535

tcg gtg gag tac tcc ttc cgc aag gtg gat ggg ccg gcc gcc gcg gcg 1785
Ser Val Glu Tyr Ser Phe Arg Lys Val Asp Gly Pro Ala Ala Ala Ala
540 545 550 555

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Gly Gln Gly Gly Ala Arg Lys Phe Asn Met Lys Met Ile
560 565

ccagggcgga ccctccctc ccctcccccg cgggccggcc gctcgcgtgt ccacctatgc 1894

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ttgtagacgc ccaaccgcag gactgttttt catcagcatg cgtctttttt gcagtttctc 2014

aagcgttttc taaagatttc aaccctctt cctgtccctg ctatggtggc tgagctgggg 2074

ggtgggggtg cgggctgcaa ggatgggggg atgggctccc gtctaccaac cgggggtggc 2134

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gactgctgcc cccaagccct gggcttcc 2222

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Val Gln Thr Arg Ala Val Ala Cys Thr Arg Arg Arg Leu Thr Ala Val
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Pro Asp Gly Ile Pro Ala Glu Thr Arg Leu Leu Glu Leu Ser Arg Asn
 25 30 35 40

Arg Ile Arg Cys Leu Asn Pro Gly Asp Leu Ala Ala Leu Pro Ala Leu
 45 50 55

Glu Glu Leu Asp Leu Ser Glu Asn Ala Ile Ala His Val Glu Pro Gly
 60 65 70

Ala Phe Ala Asn Leu Pro Arg Leu Arg Val Leu Arg Leu Arg Gly Asn
 75 80 85

Gln Leu Lys Leu Ile Pro Pro Gly Val Phe Thr Arg Leu Asp Asn Leu
 90 95 100

Thr Leu Leu Asp Leu Ser Glu Asn Lys Leu Val Ile Leu Leu Asp Tyr
 105 110 115 120

Thr Phe Gln Asp Leu His Ser Leu Arg Arg Leu Glu Val Gly Asp Asn
 125 130 135

Asp Leu Val Phe Val Ser Arg Arg Ala Phe Ala Gly Leu Leu Ala Leu
 140 145 150

Glu Glu Leu Thr Leu Glu Arg Cys Asn Leu Thr Ala Leu Ser Gly Glu
 155 160 165

Ser Leu Gly His Leu Arg Ser Leu Gly Ala Leu Arg Leu Arg His Leu
 170 175 180

Ala Ile Ala Ser Leu Glu Asp Gln Asn Phe Arg Arg Leu Pro Gly Leu
 185 190 195 200

Leu His Leu Glu Ile Asp Asn Trp Pro Leu Leu Glu Glu Val Ala Ala
 205 210 215

Gly Ser Leu Arg Gly Leu Asn Leu Thr Ser Leu Ser Val Thr His Thr
 220 225 230

Asn Ile Thr Ala Val Pro Ala Ala Ala Leu Arg His Gln Ala His Leu
 235 240 245

Thr Cys Leu Asn Leu Ser His Asn Pro Ile Ser Thr Val Pro Arg Gly
 250 255 260

Ser Phe Arg Asp Leu Val Arg Leu Arg Glu Leu His Leu Ala Gly Ala
 265 270 275 280

Leu Leu Ala Val Val Glu Pro Gln Ala Phe Leu Gly Leu Arg Gln Ile
 285 290 295

Arg Leu Leu Asn Leu Ser Asn Asn Leu Leu Ser Thr Leu Glu Glu Ser
 300 305 310

Thr Phe His Ser Val Asn Thr Leu Glu Thr Leu Arg Val Asp Gly Asn
 315 320 325

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ctg	gtc	acc	gct	gcc	ggc	aac	ttc	cgg	gac	gat	gcc	tgc	ctc	tac	tcc		1016
Leu	Val	Thr	Ala	Ala	Gly	Asn	Phe	Arg	Asp	Asp	Ala	Cys	Leu	Tyr	Ser		
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cca	gcc	tca	gct	ccc	gag	gtc	atc	aca	gtt	ggg	gcc	acc	aat	gcc	cag		1064
Pro	Ala	Ser	Ala	Pro	Glu	Val	Ile	Thr	Val	Gly	Ala	Thr	Asn	Ala	Gln		
		310				315					320						
gac	cag	ccg	gtg	acc	ctg	ggg	act	ttg	ggg	acc	aac	ttt	ggc	cgc	tgt		1112
Asp	Gln	Pro	Val	Thr	Leu	Gly	Thr	Leu	Gly	Thr	Asn	Phe	Gly	Arg	Cys		
325					330					335					340		
gtg	gac	ctc	ttt	gcc	cca	ggg	gag	gac	atc	att	ggt	gcc	tcc	agc	gac		1160
Val	Asp	Leu	Phe	Ala	Pro	Gly	Glu	Asp	Ile	Ile	Gly	Ala	Ser	Ser	Asp		
				345					350					355			
tgc	agc	acc	tgc	ttt	gtg	tca	cag	agt	ggg	aca	tca	cag	gct	gct	gcc		1208
Cys	Ser	Thr	Cys	Phe	Val	Ser	Gln	Ser	Gly	Thr	Ser	Gln	Ala	Ala	Ala		
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cac gtg gct ggc att gca gcc atg atg ctg tct gcc gag ccg gag ctc His Val Ala Gly Ile Ala Ala Met Met Leu Ser Ala Glu Pro Glu Leu 375 380 385	1256
acc ctg gcc gag ttg agg cag aga ctg atc cac ttc tct gcc aaa gat Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile His Phe Ser Ala Lys Asp 390 395 400	1304
gtc atc aat gag gcc tgg ttc cct gag gac cag cgg gta ctg acc ccc Val Ile Asn Glu Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro 405 410 415 420	1352
aac ctg gtg gcc gcc ctg ccc ccc agc acc cat ggg gca ggt tgg cag Asn Leu Val Ala Ala Leu Pro Pro Ser Thr His Gly Ala Gly Trp Gln 425 430 435	1400
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gcc aca gcc atc gcc cgc tgc gcc cca gat gag gag ctg ctg agc tgc Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp Glu Glu Leu Leu Ser Cys 455 460 465	1496
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ggg gtc tac gcc att gcc agg tgc tgc ctg cta ccc cag gcc aac tgc Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro Gln Ala Asn Cys 505 510 515	1640
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cac tgc cac caa cag ggc cac gtc ctc aca ggc tgc agc tcc cac tgg His Cys His Gln Gln Gly His Val Leu Thr Gly Cys Ser Ser His Trp 535 540 545	1736
gag gtg gag gac ctt ggc acc cac aag cgg cct gtg ctg agg cca cga Glu Val Glu Asp Leu Gly Thr His Lys Pro Pro Val Leu Arg Pro Arg 550 555 560	1784
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			600					605						610		

acc ctg act ggc tgc agt gcc ctc cct ggg acc tcc cac gtc ctg ggg 1976
Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly Thr Ser His Val Leu Gly
615 620 625

gcc tac gcc gta gac aac acg tgt gta gtc agg agc cgg gac gtc agc 2024
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Thr Thr Gly Ser Thr Ser Glu Glu Ala Val Thr Ala Val Ala Ile Cys
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tgc cgg agc cgg cac ctg gcg cag gcc ttc cag gag ctc cag 2114
Cys Arg Ser Arg His Leu Ala Gln Ala Phe Gln Glu Leu Gln
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Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
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His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
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Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
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Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
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His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
95 100 105 110

Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
115 120 125

Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
130 135 140

Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly
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Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
160 165 170

His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val
175 180 185 190

Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
195 200 205

Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
210 215 220

Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln
225 230 235

Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
240 245 250

Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
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Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu
275 280 285

Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
290 295 300

Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
305 310 315

Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
320 325 330

Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
335 340 345 350

Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly
355 360 365

Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
370 375 380

Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
385 390 395

His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
400 405 410

Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
415 420 425 430

His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
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Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp
450 455 460

Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
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Gly Glu Arg Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His
480 485 490

Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu
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Leu Pro Gln Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala
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Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
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Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
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Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
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Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
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Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val
 595 600 605

Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
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Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
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Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
 640 645 650

Thr Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Ala Gln Ala Phe
 655 660 665 670

Gln Glu Leu Gln

tcg gag tct ctg tca gat ccc agc cag ctg aac ctc tac atg aga ttt	639
Ser Glu Ser Leu Ser Asp Pro Ser Gln Leu Asn Leu Tyr Met Arg Phe	
75 80 85	
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Glu Asp Glu Ser Phe Asp Arg Leu Leu Trp Ser Ala Lys Glu Pro Ser	
90 95 100	
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Asp Ser Trp Leu Ile Ala Ser Leu Asp Leu Gln Asn Ser Ser Lys Lys	
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Phe Lys Ile Leu Ile Glu Gly Val Leu Gly Gln Gly Asn Thr Ala Ser	
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Ile Ala Leu Phe Glu Ile Lys Met Thr Thr Gly Tyr Cys Ile Glu Cys	
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Asp Phe Glu Glu Asn His Leu Cys Gly Phe Val Asn Arg Trp Asn Pro	
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Ile Leu Pro Gln Asp His Thr Phe Lys Ser Glu Leu Gly His Tyr Met	
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Tyr Val Asp Ser Val Tyr Val Lys His Phe Gln Glu Val Ala Gln Leu	
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Asn Ala Ala Trp Asn Leu Ala Glu Val Glu Phe Asn Ala Pro Tyr Pro	
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Met Glu Val Ile Phe Glu Val Ala Phe Asn Gly Pro Lys Gly Gly Tyr	

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Val	Ala	Leu	Asp	Asp	Ile	Ser	Phe	Ser	Pro	Val	His	Cys	Gln	Asn	Gln							
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aca	gaa	ctt	ctg	ttc	agt	gcc	gtg	gaa	gcc	agc	tgc	aat	ttt	gag	caa	1359						
Thr	Glu	Leu	Leu	Phe	Ser	Ala	Val	Glu	Ala	Ser	Cys	Asn	Phe	Glu	Gln							
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Val	Lys	Val	Lys	Pro	Asn	Met	Tyr	Arg	Ala	Gly	Asp	His	Thr	Thr	Gly							
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Tyr	Ile	Gly	Arg	Leu	Tyr	Gly	Pro	Ser	Leu	Pro	Gly	Asn	Leu	Gln	Tyr							
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Cys	Leu	Arg	Phe	His	Tyr	Ala	Ile	Tyr	Gly	Phe	Leu	Lys	Met	Ser	Asp							
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Thr	Leu	Ala	Val	Tyr	Ile	Phe	Glu	Glu	Asn	His	Val	Val	Gln	Glu	Lys							
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Ile	Trp	Ser	Val	Leu	Glu	Ser	Pro	Arg	Gly	Val	Trp	Met	Gln	Ala	Glu							
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Ile	Thr	Phe	Lys	Lys	Pro	Met	Pro	Thr	Lys	Val	Val	Phe	Met	Ser	Leu							
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Cys	Lys	Ser	Phe	Trp	Asp	Cys	Gly	Leu	Val	Ala	Leu	Asp	Asp	Ile	Thr							
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Ile	Gln	Leu	Gly	Ser	Cys	Ser	Ser	Ser	Glu	Lys	Leu	Pro	Pro	Pro	Pro							
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Gly	Glu	Cys	Thr	Phe	Glu	Gln	Asp	Glu	Cys	Thr	Phe	Thr	Gln	Glu	Lys							
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Arg Asn Arg Ser Ser Trp His Arg Arg Arg Gly Glu Thr Pro Thr Ser	
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Tyr Thr Gly Pro Lys Gly Asp His Thr Thr Gly Val Gly Tyr Tyr Met	
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Tyr Ile Glu Ala Ser His Met Val Tyr Gly Gln Lys Ala Arg Leu Leu	
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Ser Arg Pro Leu Arg Gly Val Ser Gly Lys His Cys Leu Thr Phe Phe	
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Tyr His Met Tyr Gly Gly Gly Thr Gly Leu Leu Ser Val Tyr Leu Lys	
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Lys Glu Glu Asp Ser Glu Glu Ser Leu Leu Trp Arg Arg Arg Gly Glu	
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Gln Ser Ile Ser Trp Leu Arg Ala Leu Ile Glu Tyr Ser Cys Glu Arg	
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Gln His Gln Ile Ile Phe Glu Ala Ile Arg Gly Val Ser Ile Arg Ser	
620 625 630	
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Gly Pro Ser Leu Pro Gly Asn Leu Gln Tyr Cys Leu Arg Phe His Tyr
385 390 395

Ala Ile Tyr Gly Phe Leu Lys Met Ser Asp Thr Leu Ala Val Tyr Ile
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Phe Glu Glu Asn His Val Val Gln Glu Lys Ile Trp Ser Val Leu Glu
415 420 425 430

Ser Pro Arg Gly Val Trp Met Gln Ala Glu Ile Thr Phe Lys Lys Pro
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Met Pro Thr Lys Val Val Phe Met Ser Leu Cys Lys Ser Phe Trp Asp
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Ser Ser Ser Glu Lys Leu Pro Pro Pro Gly Glu Cys Thr Phe Glu
480 485 490

Gln Asp Glu Cys Thr Phe Thr Gln Glu Lys Arg Asn Arg Ser Ser Trp
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His Arg Arg Arg Gly Glu Thr Pro Thr Ser Tyr Thr Gly Pro Lys Gly
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Asp His Thr Thr Gly Val Gly Tyr Tyr Met Tyr Ile Glu Ala Ser His
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Met Val Tyr Gly Gln Lys Ala Arg Leu Leu Ser Arg Pro Leu Arg Gly
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Arg Ala Leu Ile Glu Tyr Ser Cys Glu Arg Gln His Gln Ile Ile Phe
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Glu Ala Ile Arg Gly Val Ser Ile Arg Ser Asp Ile Ala Ile Asp Asp
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Thr Ser Leu Ala Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr	
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Gln Ile Leu Gln Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser	
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Ala Ile His Gln Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro	
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Ser Lys Asp Leu Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys	
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Glu Leu Gln Leu Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr	
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Glu Ala Glu Val Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln	
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gcg agg atc aac agc cat gtg aaa aag aag acc caa ggg aag gtt gta	699
Ala Arg Ile Asn Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val	
155 160 165	
gac ata atc caa ggc ctt gac ctt ctg acg gcc atg gtt ctg gtg aat	747
Asp Ile Ile Gln Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn	
170 175 180	
cac att ttc ttt aaa gcc aag tgg gag aag ccc ttt cac ctt gaa tat	795
His Ile Phe Phe Lys Ala Lys Trp Glu Lys Pro Phe His Leu Glu Tyr	
185 190 195 200	
aca aga aag aac ttc cca ttc ctg gtg ggc gag cag gtc act gtg caa	843
Thr Arg Lys Asn Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val Gln	
205 210 215	
gtc ccc atg atg cac cag aaa gag cag ttc gct ttt ggg gtg gat aca	891
Val Pro Met Met His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr	
220 225 230	
gag ctg aac tgc ttt gtg ctg cag atg gat tac aag gga gat gcc gtg	939
Glu Leu Asn Cys Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val	
235 240 245	

gcc ttc ttt gtc ctc cct agc aag ggc aag atg agg caa ctg gaa cag 987
 Ala Phe Phe Val Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln
 250 255 260

gcc ttg tca gcc aga aca ctg ata aag tgg agc cac tca ctc cag aaa 1035
 Ala Leu Ser Ala Arg Thr Leu Ile Lys Trp Ser His Ser Leu Gln Lys
 265 270 275 280

agg tgg ata gag gtg ttc atc ccc aga ttt tcc att tct gcc tcc tac 1083
 Arg Trp Ile Glu Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr
 285 290 295

aat ctg gaa acc atc ctc ccg aag atg ggc atc caa aat gcc ttt gac 1131
 Asn Leu Glu Thr Ile Leu Pro Lys Met Gly Ile Gln Asn Ala Phe Asp
 300 305 310

aaa aat gct gat ttt tct gga att gca aag aga gac tcc ctg cag gtt 1179
 Lys Asn Ala Asp Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val
 315 320 325

tct aaa gca acc cac aag gct gtg ctg gat gtc agt gaa gag ggc act 1227
 Ser Lys Ala Thr His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr
 330 335 340

gag gcc aca gca gct acc acc acc aag ttc ata gtc cga tcg aag gat 1275
 Glu Ala Thr Ala Ala Thr Thr Lys Phe Ile Val Arg Ser Lys Asp
 345 350 355 360

ggt ccc tct tac ttc act gtc tcc ttc aat agg acc ttc ctg atg atg 1323
 Gly Pro Ser Tyr Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met
 365 370 375

att aca aat aaa gcc aca gac ggt att ctc ttt cta ggg aaa gtg gaa 1371
 Ile Thr Asn Lys Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu
 380 385 390

aat ccc act aaa tcc taggtgggaa atggcctgtt aactgatggc acattgctaa 1426
 Asn Pro Thr Lys Ser
 395

tgcacaagaa ataacaaacc acatcctctt tctgttctga gggtgcattt gaccccagtg 1486

ggagctggat tcgctggcag ggatgccacc ttccaaggct caatcaccaa accatcaaca 1546

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<213> Homo sapiens

<400> 24

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 -1 1 5 10

Pro Ser Ser Thr Lys Ser Thr Pro Ala Ser Gln Val Tyr Ser Leu Asn
 15 20 25

Thr Asp Phe Ala Phe Arg Leu Tyr Arg Arg Leu Val Leu Glu Thr Pro
 30 35 40

Ser Gln Asn Ile Phe Phe Ser Pro Val Ser Val Ser Thr Ser Leu Ala
 45 50 55 60

Met Leu Ser Leu Gly Ala His Ser Val Thr Lys Thr Gln Ile Leu Gln
 65 70 75

Gly Leu Gly Phe Asn Leu Thr His Thr Pro Glu Ser Ala Ile His Gln
 80 85 90

Gly Phe Gln His Leu Val His Ser Leu Thr Val Pro Ser Lys Asp Leu
 95 100 105

Thr Leu Lys Met Gly Ser Ala Leu Phe Val Lys Lys Glu Leu Gln Leu
 110 115 120

Gln Ala Asn Phe Leu Gly Asn Val Lys Arg Leu Tyr Glu Ala Glu Val
 125 130 135 140

Phe Ser Thr Asp Phe Ser Asn Pro Ser Ile Ala Gln Ala Arg Ile Asn
 145 150 155

Ser His Val Lys Lys Lys Thr Gln Gly Lys Val Val Asp Ile Ile Gln
 160 165 170

Gly Leu Asp Leu Leu Thr Ala Met Val Leu Val Asn His Ile Phe Phe
 175 180 185

Lys Ala Lys Trp Glu Lys Pro Phe His Leu Glu Tyr Thr Arg Lys Asn
 190 195 200

Phe Pro Phe Leu Val Gly Glu Gln Val Thr Val Gln Val Pro Met Met
 205 210 215 220

His Gln Lys Glu Gln Phe Ala Phe Gly Val Asp Thr Glu Leu Asn Cys
 225 230 235

Phe Val Leu Gln Met Asp Tyr Lys Gly Asp Ala Val Ala Phe Phe Val
 240 245 250

Leu Pro Ser Lys Gly Lys Met Arg Gln Leu Glu Gln Ala Leu Ser Ala
 255 260 265

Arg Thr Leu Ile Lys Trp Ser His Ser Leu Gln Lys Arg Trp Ile Glu
 270 275 280

Val Phe Ile Pro Arg Phe Ser Ile Ser Ala Ser Tyr Asn Leu Glu Thr
 285 290 295 300

Ile Leu Pro Lys Met Gly Ile Gln Asn Ala Phe Asp Lys Asn Ala Asp
 305 310 315

Phe Ser Gly Ile Ala Lys Arg Asp Ser Leu Gln Val Ser Lys Ala Thr
 320 325 330

His Lys Ala Val Leu Asp Val Ser Glu Glu Gly Thr Glu Ala Thr Ala
 335 340 345

Ala Thr Thr Thr Lys Phe Ile Val Arg Ser Lys Asp Gly Pro Ser Tyr
 350 355 360

Phe Thr Val Ser Phe Asn Arg Thr Phe Leu Met Met Ile Thr Asn Lys
 365 370 375 380

Ala Thr Asp Gly Ile Leu Phe Leu Gly Lys Val Glu Asn Pro Thr Lys
 385 390 395

Ser


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90 95 100 105	
ttt gac aac cgg ctg acc acg gtg ccc acg cag gcc ttc gag tac ctg	603
Phe Asp Asn Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu	
110 115 120	
tcc aag ctg cgg gag ctc tgg ctg cgg aac aac ccc atc gag agc atc	651
Ser Lys Leu Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile	
125 130 135	
ccc tcc tac gcc ttc aac cgc gtg ccc tcg ctg cgg cgc ctg gac ctg	699
Pro Ser Tyr Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu	
140 145 150	
ggc gag ctc aag cgg ctg gaa tac atc tcg gag gcg gcc ttc gag ggg	747
Gly Glu Leu Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly	
155 160 165	
ctg gtc aac ctg cgc tac ctc aac ctg ggc atg tgc aac ctc aag gac	795
Leu Val Asn Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp	
170 175 180 185	
atc ccc aac ctg acg gcc ctg gtg cgc ctg gag gag ctg gag ctg tcg	843
Ile Pro Asn Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser	
190 195 200	
ggc aac cgg ctg gac ctg atc cgc ccg ggc tcc ttc cag ggt ctc acc	891
Gly Asn Arg Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr	
205 210 215	
agc ctg cgc aag ctg tgg ctc atg cac gcc cag gta gcc acc atc gag	939
Ser Leu Arg Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu	
220 225 230	
cgc aac gcc ttc gac gac ctc aag tcg ctg gag gag ctc aac ctg tcc	987
Arg Asn Ala Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser	
235 240 245	
cac aac aac ctg atg tcg ctg ccc cac gac ctc ttc acg ccc ctg cac	1035
His Asn Asn Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His	
250 255 260 265	
cgc ctc gag cgc gtg cac ctc aac cac aac ccc tgg cat tgc aac tgc	1083
Arg Leu Glu Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys	
270 275 280	
gac gtg ctc tgg ctg agc tgg tgg ctc aag gag acg gtg ccc agc aac	1131
Asp Val Leu Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn	
285 290 295	

acg acg tgc tgc gcc cgc tgt cat gcg ccc gcc ggc ctc aag ggg cgc Thr Thr Cys Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg 300 305 310	1179
tac att ggg gag ctg gac cag tcg cat ttc acc tgc tat gcg ccc gtc Tyr Ile Gly Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val 315 320 325	1227
atc gtg gag ccg ccc acg gac ctc aac gtc acc gag ggc atg gct gcc Ile Val Glu Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala 330 335 340 345	1275
gag ctc aaa tgc cgc acg ggc acc tcc atg acc tcc gtc aac tgg ctg Glu Leu Lys Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu 350 355 360	1323
acg ccc aac ggc acc ctc atg acc cac ggc tcc tac cgc gtg cgc atc Thr Pro Asn Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile 365 370 375	1371
tcc gtc ctg cat gac ggc acg ctt aac ttc acc aac gtc acc gtg cag Ser Val Leu His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln 380 385 390	1419
gac acg ggc cag tac acg tgc atg gtg acg aac tca gcc ggc aac acc Asp Thr Gly Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr 395 400 405	1467
acc gcc tcg gcc acg ctc aac gtc tcg gcc gtg gac ccc gtg gcg gcc Thr Ala Ser Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala 410 415 420 425	1515
ggg ggc acc ggc agc ggc ggg ggc ggc cct ggg ggc agt ggt ggt gtt Gly Gly Thr Gly Ser Gly Gly Gly Gly Pro Gly Gly Ser Gly Gly Val 430 435 440	1563
gga ggg ggc agt ggc ggc tac acc tac ttc acc acg gtg acc gtg gag Gly Gly Gly Ser Gly Gly Tyr Thr Tyr Phe Thr Thr Val Thr Val Glu 445 450 455	1611
acc ctg gag acg cag ccc gga gag gag gcc ctg cag ccg cgg ggg acg Thr Leu Glu Thr Gln Pro Gly Glu Glu Ala Leu Gln Pro Arg Gly Thr 460 465 470	1659
gag aag gaa ccg cca ggg ccc acg aca gac ggt gtc tgg ggt ggg ggc Glu Lys Glu Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Gly 475 480 485	1707
cgg cct ggg gac gcg gcc ggc cct gcc tcg tct tct acc acg gca ccc Arg Pro Gly Asp Ala Ala Gly Pro Ala Ser Ser Ser Thr Thr Ala Pro 490 495 500 505	1755

gcc ccg cgc tcc tcg cgg ccc acg gag aag gcg ttc acg gtg ccc atc 1803
 Ala Pro Arg Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile
 510 515 520

acg gat gtg acg gag aac gcc ctc aag gac ctg gac gac gtc atg aag 1851
 Thr Asp Val Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys
 525 530 535

acc acc aaa atc atc atc ggc tgc ttc gtg gcc atc acg ttc atg gcc 1899
 Thr Thr Lys Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala
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gcg gtg atg ctc gtg gcc ttc tac aag ctg cgc aag cag cac cag ctc 1947
 Ala Val Met Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu
 555 560 565

cac aag cac cac ggg ccc acg cgc acc gtg gag atc atc aac gtg gag 1995
 His Lys His His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu
 570 575 580 585

gac gag ctg ccc gcc gcc tcg gcc gtg tcc gtg gcc gcc gcg gcc gcc 2043
 Asp Glu Leu Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala Ala
 590 595 600

gtg gcc agt ggg ggt ggt gtg ggc ggg gac agc cac ctg gcc ctg ccc 2091
 Val Ala Ser Gly Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro
 605 610 615

gcc ctg gag cga gac cac ctc aac cac cac cac tac gtg gct gcc gcc 2139
 Ala Leu Glu Arg Asp His Leu Asn His His His Tyr Val Ala Ala Ala
 620 625 630

ttc aag gcg cac tac agc agc aac ccc agc ggc ggg ggc tgc ggg ggc 2187
 Phe Lys Ala His Tyr Ser Ser Asn Pro Ser Gly Gly Gly Cys Gly Gly
 635 640 645

aaa ggc ccg cct ggc ctc aac tcc atc cac gaa cct ctg ctc ttc aag 2235
 Lys Gly Pro Pro Gly Leu Asn Ser Ile His Glu Pro Leu Leu Phe Lys
 650 655 660 665

agc ggc tcc aag gag aac gtg caa gag acg cag atc tgaggcggcg 2281
 Ser Gly Ser Lys Glu Asn Val Gln Glu Thr Gln Ile
 670 675

gggccggggcg ggcgaggggc gtggagcccc ccaccaggt cccagcccg ggcgagcctg 2341

accgggaccc ctccctccca cagcccagcc caccttcttg gaccacgcag ggaattgggg 2401

agaggtggct tccagcccca tctggggctc ggacccccag taaggacagg gtggggctcc 2461

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cgttccgggc ccgccgcctt ccaggggaga gaggagcttt ctccaggggt gtcctttccc 2641
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Met Ser Trp Pro His Gly Ala Leu Leu Phe Leu Trp Leu Phe Ser Pro
 -20 -15 -10 -5

Pro Leu Gly Ala Gly Gly Gly Gly Val Ala Val Thr Ser Ala Ala Gly
 -1 1 5 10

Gly Gly Ser Pro Pro Ala Thr Ser Cys Pro Val Ala Cys Ser Cys Ser
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Asn Gln Ala Ser Arg Val Ile Cys Thr Arg Arg Asp Leu Ala Glu Val
 30 35 40

Pro Ala Ser Ile Pro Val Asn Thr Arg Tyr Leu Asn Leu Gln Glu Asn
 45 50 55 60

Gly Ile Gln Val Ile Arg Thr Asp Thr Phe Lys His Leu Arg His Leu
 65 70 75

Glu Ile Leu Gln Leu Ser Lys Asn Leu Val Arg Lys Ile Glu Val Gly
 80 85 90

Ala Phe Asn Gly Leu Pro Ser Leu Asn Thr Leu Glu Leu Phe Asp Asn
 95 100 105

Arg Leu Thr Thr Val Pro Thr Gln Ala Phe Glu Tyr Leu Ser Lys Leu
 110 115 120

Arg Glu Leu Trp Leu Arg Asn Asn Pro Ile Glu Ser Ile Pro Ser Tyr
 125 130 135 140

Ala Phe Asn Arg Val Pro Ser Leu Arg Arg Leu Asp Leu Gly Glu Leu
 145 150 155

Lys Arg Leu Glu Tyr Ile Ser Glu Ala Ala Phe Glu Gly Leu Val Asn
 160 165 170

Leu Arg Tyr Leu Asn Leu Gly Met Cys Asn Leu Lys Asp Ile Pro Asn
 175 180 185

Leu Thr Ala Leu Val Arg Leu Glu Glu Leu Glu Leu Ser Gly Asn Arg
 190 195 200

Leu Asp Leu Ile Arg Pro Gly Ser Phe Gln Gly Leu Thr Ser Leu Arg
 205 210 215 220

Lys Leu Trp Leu Met His Ala Gln Val Ala Thr Ile Glu Arg Asn Ala
 225 230 235

Phe Asp Asp Leu Lys Ser Leu Glu Glu Leu Asn Leu Ser His Asn Asn
 240 245 250

Leu Met Ser Leu Pro His Asp Leu Phe Thr Pro Leu His Arg Leu Glu
 255 260 265

Arg Val His Leu Asn His Asn Pro Trp His Cys Asn Cys Asp Val Leu
 270 275 280

Trp Leu Ser Trp Trp Leu Lys Glu Thr Val Pro Ser Asn Thr Thr Cys
 285 290 295 300

Cys Ala Arg Cys His Ala Pro Ala Gly Leu Lys Gly Arg Tyr Ile Gly
 305 310 315

Glu Leu Asp Gln Ser His Phe Thr Cys Tyr Ala Pro Val Ile Val Glu
 320 325 330

Pro Pro Thr Asp Leu Asn Val Thr Glu Gly Met Ala Ala Glu Leu Lys
 335 340 345

Cys Arg Thr Gly Thr Ser Met Thr Ser Val Asn Trp Leu Thr Pro Asn
 350 355 360

Gly Thr Leu Met Thr His Gly Ser Tyr Arg Val Arg Ile Ser Val Leu
 365 370 375 380

His Asp Gly Thr Leu Asn Phe Thr Asn Val Thr Val Gln Asp Thr Gly
 385 390 395

Gln Tyr Thr Cys Met Val Thr Asn Ser Ala Gly Asn Thr Thr Ala Ser
 400 405 410

Ala Thr Leu Asn Val Ser Ala Val Asp Pro Val Ala Ala Gly Gly Thr
 415 420 425

Gly Ser Gly Gly Gly Gly Pro Gly Gly Ser Gly Gly Val Gly Gly Gly
 430 435 440

Ser Gly Gly Tyr Thr Tyr Phe Thr Thr Val Thr Val Glu Thr Leu Glu
 445 450 455 460

Thr Gln Pro Gly Glu Glu Ala Leu Gln Pro Arg Gly Thr Glu Lys Glu
 465 470 475

Pro Pro Gly Pro Thr Thr Asp Gly Val Trp Gly Gly Gly Arg Pro Gly
 480 485 490

Asp Ala Ala Gly Pro Ala Ser Ser Ser Thr Thr Ala Pro Ala Pro Arg
 495 500 505

Ser Ser Arg Pro Thr Glu Lys Ala Phe Thr Val Pro Ile Thr Asp Val
 510 515 520

Thr Glu Asn Ala Leu Lys Asp Leu Asp Asp Val Met Lys Thr Thr Lys
 525 530 535 540

Ile Ile Ile Gly Cys Phe Val Ala Ile Thr Phe Met Ala Ala Val Met
 545 550 555

Leu Val Ala Phe Tyr Lys Leu Arg Lys Gln His Gln Leu His Lys His
 560 565 570

His Gly Pro Thr Arg Thr Val Glu Ile Ile Asn Val Glu Asp Glu Leu
 575 580 585

Pro Ala Ala Ser Ala Val Ser Val Ala Ala Ala Ala Val Ala Ser
 590 595 600

Gly Gly Gly Val Gly Gly Asp Ser His Leu Ala Leu Pro Ala Leu Glu
 605 610 615 620

Arg Asp His Leu Asn His His His Tyr Val Ala Ala Ala Phe Lys Ala
 625 630 635

His Tyr Ser Ser Asn Pro Ser Gly Gly Gly Cys Gly Gly Lys Gly Pro
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Pro Gly Leu Asn Ser Ile His Glu Pro Leu Leu Phe Lys Ser Gly Ser
 655 660 665

Lys Glu Asn Val Gln Glu Thr Gln Ile
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gcg gct cgg ctg cac ggg gcg cgt ggt ctg cgc tat ttg ttg ctg cag Ala Ala Arg Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Leu Gln 190 195 200 205	785
cac aac cag ctg ggg agc tca ggg ctg ccc gcc ggg gct ctg cgg ccg His Asn Gln Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg Pro 210 215 220	833
ctg cgg ggc ctg cac acg ctg cac ctc tat ggc aat ggg ctg gac cgc Leu Arg Gly Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp Arg 225 230 235	881
gtg cct cca gcc ctg ccc cgc cgc ctg cgt gcc ctg gtg ctg ccc cac Val Pro Pro Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu Pro His 240 245 250	929
aac cac gtg gcc gcg ctg ggt gcc cgt gac ctg gtc gcc aca ccg ggc Asn His Val Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr Pro Gly 255 260 265	977
ctg acg gag ctt aac ctg gcc tat aac cgc ctg gcc agc gcc cgt gtg Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala Arg Val 270 275 280 285	1025
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gca ggg aat cag cta acc cgg ctg ccc atg ggc ctg ccc act ggc ctg Ala Gly Asn Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr Gly Leu 305 310 315	1121
cgc acc ctg cag ctg caa cgc aac cag ctg cgg atg ctc gag ccc gag Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu Pro Glu 320 325 330	1169
cct ctg gcc ggc ctg gac caa ctg cgg gag ctc agc ctg gcg cac aac Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala His Asn 335 340 345	1217
cgg ctc cgg gtc ggc gac atc ggg cca ggc acc tgg cat gag ctc caa Arg Leu Arg Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu Leu Gln 350 355 360 365	1265

gcc ctc cag gtc agg cac agg ctg gtt agc cac act gtc ccc agg gcc 1313
 Ala Leu Gln Val Arg His Arg Leu Val Ser His Thr Val Pro Arg Ala
 370 375 380

cct cca tcc ccc tgc ctg ccc tgc cac gtc cca aac att cta gtt agc 1361
 Pro Pro Ser Pro Cys Leu Pro Cys His Val Pro Asn Ile Leu Val Ser
 385 390 395

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 Trp

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Pro His Leu Gly Glu Ser Leu Gln Pro Leu Pro Arg Ala Cys Pro Leu
 10 15 20

Arg Cys Ser Cys Pro Arg Val Asp Thr Val Asp Cys Asp Gly Leu Asp
 25 30 35

Leu Arg Val Phe Pro Asp Asn Ile Thr Arg Ala Ala Gln His Leu Ser
 40 45 50 55

Leu Gln Asn Asn Gln Leu Gln Glu Leu Pro Tyr Asn Glu Leu Ser Arg
 60 65 70

Leu Ser Gly Leu Arg Thr Leu Asn Leu His Asn Asn Leu Ile Ser Ser
 75 80 85

Glu Gly Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His
 90 95 100

Leu Cys Val Ala His Asn Lys Asn Asn Leu Ile Ser Lys Val Pro Arg
 105 110 115

Gly Ala Leu Ser Arg Gln Thr Gln Leu Arg Glu Leu Tyr Leu Gln His
120 125 130 135

Asn Gln Leu Thr Asp Ser Gly Leu Asp Ala Thr Thr Phe Ser Lys Leu
140 145 150

His Ser Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu Thr Thr Val
155 160 165

Pro Ala Gly Leu Pro Arg Thr Leu Ala Ile Leu His Leu Gly Arg Asn
170 175 180

Arg Ile Arg Gln Val Glu Ala Ala Arg Leu His Gly Ala Arg Gly Leu
185 190 195

Arg Tyr Leu Leu Leu Gln His Asn Gln Leu Gly Ser Ser Gly Leu Pro
200 205 210 215

Ala Gly Ala Leu Arg Pro Leu Arg Gly Leu His Thr Leu His Leu Tyr
220 225 230

Gly Asn Gly Leu Asp Arg Val Pro Pro Ala Leu Pro Arg Arg Leu Arg
235 240 245

Ala Leu Val Leu Pro His Asn His Val Ala Ala Leu Gly Ala Arg Asp
250 255 260

Leu Val Ala Thr Pro Gly Leu Thr Glu Leu Asn Leu Ala Tyr Asn Arg
265 270 275

Leu Ala Ser Ala Arg Val His His Arg Ala Phe Arg Arg Leu Arg Ala
280 285 290 295

Leu Arg Ser Leu Asp Leu Ala Gly Asn Gln Leu Thr Arg Leu Pro Met
300 305 310

Gly Leu Pro Thr Gly Leu Arg Thr Leu Gln Leu Gln Arg Asn Gln Leu
315 320 325

Arg Met Leu Glu Pro Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg Glu
 330 335 340

Leu Ser Leu Ala His Asn Arg Leu Arg Val Gly Asp Ile Gly Pro Gly
 345 350 355

Thr Trp His Glu Leu Gln Ala Leu Gln Val Arg His Arg Leu Val Ser
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His Thr Val Pro Arg Ala Pro Pro Ser Pro Cys Leu Pro Cys His Val
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Pro Asn Ile Leu Val Ser Trp
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 Val Leu Trp Ala Ser Cys Pro Pro Cys Ser Gly Arg Lys Gly Pro Pro
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 Ala Ala Leu Thr Leu Pro Arg Val Gln Cys Arg Ala Ser Arg Tyr Pro
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atc gcc gtg gat tgc tcc tgg acc ctg ccg cct gct cca aac tcc acc 195
 Ile Ala Val Asp Cys Ser Trp Thr Leu Pro Pro Ala Pro Asn Ser Thr
 25 30 35 40

agc ccc gtg tcc ttc att gcc acg tac agg tcg gag agc ctg gaa ggg 243
 Ser Pro Val Ser Phe Ile Ala Thr Tyr Arg Ser Glu Ser Leu Glu Gly
 45 50 55

ggc ctc agg gac act gga ctt cct gga gag ccc aga act ctg gcc ctg 291
 Gly Leu Arg Asp Thr Gly Leu Pro Gly Glu Pro Arg Thr Leu Ala Leu
 60 65 70

aga gcc ctg ggg tca gga aaa ctg gag acc ccg aca tcc tgaaccccag 340
 Arg Ala Leu Gly Ser Gly Lys Leu Glu Thr Pro Thr Ser
 75 80 85

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa gaaaaaaaaa aaaaaa 445

<210> 30
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 <213> Homo sapiens

<400> 30

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 -15 -10 -5

Pro Cys Ser Gly Arg Lys Gly Pro Pro Ala Ala Leu Thr Leu Pro Arg
 -1 1 5 10 15

Val Gln Cys Arg Ala Ser Arg Tyr Pro Ile Ala Val Asp Cys Ser Trp
 20 25 30

Thr Leu Pro Pro Ala Pro Asn Ser Thr Ser Pro Val Ser Phe Ile Ala
 35 40 45

Thr Tyr Arg Ser Glu Ser Leu Glu Gly Gly Leu Arg Asp Thr Gly Leu
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Pro Gly Glu Pro Arg Thr Leu Ala Leu Arg Ala Leu Gly Ser Gly Lys
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Leu Glu Thr Pro Thr Ser
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<210> 31
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<222> (79)..()

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Met Val Ser Pro Arg Met Ser Gly Leu Leu Ser Gln Thr Val Ile Leu
      -25                      -20                      -15

gcg ctc att ttc ctc ccc cag aca cgg ccc gct ggc gtc ttc gag ctg      96
Ala Leu Ile Phe Leu Pro Gln Thr Arg Pro Ala Gly Val Phe Glu Leu
      -10                      -5                      -1 1                      5

cag atc cac tct ttc ggg ccg ggt cca ggc cct ggg gcc ccg cgg tcc      144
Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
              10                      15                      20

ccc tgc agc gcc cgg ctc ccc tgc cgc ctc ttc ttc aga gtc tgc ctg      192
Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
              25                      30                      35

aag cct ggg ctc tca gag gag gcc gcc gag tcc ccg tgc gcc ctg ggc      240
Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
      40                      45                      50

gcg gcg ctg agt gcg cgc gga ccg gtc tac acc gag cag ccc gga gcg      288
Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
      55                      60                      65                      70

ccc gcg cct gat ctc cca ctg ccc gac ggc ctc ttg cag gtg ccc ttc      336
Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
              75                      80                      85

cgg gac gcc tgg cct ggc acc ttc tct ttc atc atc gaa acc tgg aga      384
Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
              90                      95                      100

gag gag tta gga gac cag att gga ggg ccc gcc tgg agc ctg ctg gcg      432
Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
              105                      110                      115

cgc gtg gct ggc agg cgg cgc ttg gca gcc gga ggc ccg tgg gcc cgg      480
Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
      120                      125                      130

gac att cag cgc gca ggc gcc tgg gag ctg cgc tgc tcg tac cgc gcg      528
Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Cys Ser Tyr Arg Ala
      135                      140                      145                      150

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ccg tgc gag ccg cct gcg gtc ggg acc gcg tgc acg cgc ctc tgc cgt	576
Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg	
155 160 165	
ccg cgc agc gcc ccc tcg cgg tgc ggt ccg gga ctg cgc ccc tgc gca	624
Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala	
170 175 180	
ccg ctc gag gac gaa tgt gag gcg ccg ccg gtg tgc cga gca ggc tgc	672
Pro Leu Glu Asp Glu Cys Glu Ala Pro Pro Val Cys Arg Ala Gly Cys	
185 190 195	
agc cct gag cat ggc ttc tgt gaa cag ccc ggt gaa tgc cga tgc cta	720
Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu	
200 205 210	
gag ggc tgg act gga ccc ctc tgc acg gtc cct gtc tcc acc agc agc	768
Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser	
215 220 225 230	
tgc ctc agc ccc agg ggc ccg tcc tct gct acc acc gga tgc ctt gtc	816
Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val	
235 240 245	
cct ggg cct ggg ccc tgt gac ggg aac ccg tgt gcc aat gga ggc agc	864
Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser	
250 255 260	
tgt agt gag aca ccc agg tcc ttt gaa tgc acc tgc ccg cgt ggg ttc	912
Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe	
265 270 275	
tac ggg ctg cgg tgt gag gtg agc ggg gtg aca tgt gca gat gga ccc	960
Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro	
280 285 290	
tgc ttc aac ggc ggc ttg tgt gtc ggg ggt gca gac cct gac tct gcc	1008
Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala	
295 300 305 310	
tac atc tgc cac tgc cca cct ggt ttc caa ggc tcc aac tgt gag aag	1056
Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys	
315 320 325	
agg gtg gac cgg tgc agc ctg cag cca tgc cgc aat ggc gga ctc tgc	1104
Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys	
330 335 340	
ctg gac ctg ggc cac gcc ctg cgc tgc cgc tgc cgc gcc ggc ttc gcg	1152
Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala	
345 350 355	

ggt cct cgc tgc gag cac gac ctg gac gac tgc gcg ggc cgc gcc tgc 1200
 Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
 360 365 370

gct aac ggc ggc acg tgt gtg gag ggc ggc ggc gcg cac cgc tgc tcc 1248
 Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
 375 380 385 390

tgc gcg ctg ggc ttc ggc ggc cgc gac tgc cgc gag cgc gcg gac ccg 1296
 Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
 395 400 405

tgc gcc gcg cgc ccc tgt gct cac ggc ggc cgc tgc tac gcc cac ttc 1344
 Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
 410 415 420

tcc ggc ctc gtc tgc gct tgc gct ccc ggc tac atg gga gcg cgg tgt 1392
 Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
 425 430 435

gag ttc cca gtg cac ccc gac ggc gca agc gcc ttg ccc gcg gcc ccg 1440
 Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
 440 445 450

ccg ggc ctc agg ccc ggg gac cct cag cgc tac ctt ttg cct ccg gct 1488
 Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
 455 460 465 470

ctg gga ctg ctc gtg gcc gcg ggc gtg gcc ggc gct gcg ctc ttg ctg 1536
 Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
 475 480 485

gtc cac gtg cgc cgc cgt ggc cac tcc cag gat gct ggg tct cgc ttg 1584
 Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
 490 495 500

ctg gct ggg acc ccg gag ccg tca gtc cac gca ctc ccg gat gca ctc 1632
 Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
 505 510 515

aac aac cta agg acg cag gag ggt tcc ggg gat ggt ccg agc tcg tcc 1680
 Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
 520 525 530

gta gat tgg aat cgc cct gaa gat gta gac cct caa ggg att tat gtc 1728
 Val Asp Trp Asn Arg Pro Glu Asp Val Asp Pro Gln Gly Ile Tyr Val
 535 540 545 550

ata tct gct cct tcc atc tac gct cgg gag gcc tgacgcgtct cctccatccg 1781
 Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Ala
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aggctttgga gttcaat

1858

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<211> 587

<212> PRT

<213> Homo sapiens

<400> 32

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 -10 -5 -1 1 5

Gln Ile His Ser Phe Gly Pro Gly Pro Gly Pro Gly Ala Pro Arg Ser
 10 15 20

Pro Cys Ser Ala Arg Leu Pro Cys Arg Leu Phe Phe Arg Val Cys Leu
 25 30 35

Lys Pro Gly Leu Ser Glu Glu Ala Ala Glu Ser Pro Cys Ala Leu Gly
 40 45 50

Ala Ala Leu Ser Ala Arg Gly Pro Val Tyr Thr Glu Gln Pro Gly Ala
 55 60 65 70

Pro Ala Pro Asp Leu Pro Leu Pro Asp Gly Leu Leu Gln Val Pro Phe
 75 80 85

Arg Asp Ala Trp Pro Gly Thr Phe Ser Phe Ile Ile Glu Thr Trp Arg
 90 95 100

Glu Glu Leu Gly Asp Gln Ile Gly Gly Pro Ala Trp Ser Leu Leu Ala
 105 110 115

Arg Val Ala Gly Arg Arg Arg Leu Ala Ala Gly Gly Pro Trp Ala Arg
 120 125 130

Asp Ile Gln Arg Ala Gly Ala Trp Glu Leu Arg Cys Ser Tyr Arg Ala
 135 140 145 150

Arg Cys Glu Pro Pro Ala Val Gly Thr Ala Cys Thr Arg Leu Cys Arg
 155 160 165

Pro Arg Ser Ala Pro Ser Arg Cys Gly Pro Gly Leu Arg Pro Cys Ala
 170 175 180

Pro Leu Glu Asp Glu Cys Glu Ala Pro Pro Val Cys Arg Ala Gly Cys
 185 190 195

Ser Pro Glu His Gly Phe Cys Glu Gln Pro Gly Glu Cys Arg Cys Leu
 200 205 210

Glu Gly Trp Thr Gly Pro Leu Cys Thr Val Pro Val Ser Thr Ser Ser
 215 220 225 230

Cys Leu Ser Pro Arg Gly Pro Ser Ser Ala Thr Thr Gly Cys Leu Val
 235 240 245

Pro Gly Pro Gly Pro Cys Asp Gly Asn Pro Cys Ala Asn Gly Gly Ser
 250 255 260

Cys Ser Glu Thr Pro Arg Ser Phe Glu Cys Thr Cys Pro Arg Gly Phe
 265 270 275

Tyr Gly Leu Arg Cys Glu Val Ser Gly Val Thr Cys Ala Asp Gly Pro
 280 285 290

Cys Phe Asn Gly Gly Leu Cys Val Gly Gly Ala Asp Pro Asp Ser Ala
 295 300 305 310

Tyr Ile Cys His Cys Pro Pro Gly Phe Gln Gly Ser Asn Cys Glu Lys
 315 320 325

Arg Val Asp Arg Cys Ser Leu Gln Pro Cys Arg Asn Gly Gly Leu Cys
 330 335 340

Leu Asp Leu Gly His Ala Leu Arg Cys Arg Cys Arg Ala Gly Phe Ala
 345 350 355

Gly Pro Arg Cys Glu His Asp Leu Asp Asp Cys Ala Gly Arg Ala Cys
 360 365 370

Ala Asn Gly Gly Thr Cys Val Glu Gly Gly Gly Ala His Arg Cys Ser
 375 380 385 390

Cys Ala Leu Gly Phe Gly Gly Arg Asp Cys Arg Glu Arg Ala Asp Pro
 395 400 405

Cys Ala Ala Arg Pro Cys Ala His Gly Gly Arg Cys Tyr Ala His Phe
 410 415 420

Ser Gly Leu Val Cys Ala Cys Ala Pro Gly Tyr Met Gly Ala Arg Cys
 425 430 435

Glu Phe Pro Val His Pro Asp Gly Ala Ser Ala Leu Pro Ala Ala Pro
 440 445 450

Pro Gly Leu Arg Pro Gly Asp Pro Gln Arg Tyr Leu Leu Pro Pro Ala
 455 460 465 470

Leu Gly Leu Leu Val Ala Ala Gly Val Ala Gly Ala Ala Leu Leu Leu
 475 480 485

Val His Val Arg Arg Arg Gly His Ser Gln Asp Ala Gly Ser Arg Leu
 490 495 500

Leu Ala Gly Thr Pro Glu Pro Ser Val His Ala Leu Pro Asp Ala Leu
 505 510 515

Asn Asn Leu Arg Thr Gln Glu Gly Ser Gly Asp Gly Pro Ser Ser Ser
 520 525 530

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 535 540 545 550

Ile Ser Ala Pro Ser Ile Tyr Ala Arg Glu Ala
 555 560

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<222> (25) .. (1926)
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gac acc agc ata cag agt gac cac cgg gaa atc gag ggc agg gtc atg Asp Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly Arg Val Met 170 175 180	627
gtc acc gac ttc gag aat gtg ccc gag gag gac ggg acc cgc ttc cac Val Thr Asp Phe Glu Asn Val Pro Glu Glu Asp Gly Thr Arg Phe His 185 190 195	675
aga cag gcc agc aag tgt gac agt cat ggc acc cac ctg gca ggg gtg Arg Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val 200 205 210 215	723
gtc agc ggc cgg gat gcc ggc gtg gcc aag ggt gcc agc atg cgc agc Val Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Ala Ser Met Arg Ser 220 225 230	771
ctg cgc gtg ctc aac tgc caa ggg aag ggc acg gtt agc ggc acc ctc Leu Arg Val Leu Asn Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu 235 240 245	819
ata ggc ctg gag ttt att cgg aaa agc cag ctg gtc cag cct gtg ggg Ile Gly Leu Glu Phe Ile Arg Lys Ser Gln Leu Val Gln Pro Val Gly 250 255 260	867
cca ctg gtg gtg ctg ctg ccc ctg gcg ggt ggg tac agc cgc gtc ctc Pro Leu Val Val Leu Leu Pro Leu Ala Gly Gly Tyr Ser Arg Val Leu 265 270 275	915
aac gcc gcc tgc cag cgc ctg gcg agg gct ggg gtc gtg ctg gtc acc Asn Ala Ala Cys Gln Arg Leu Ala Arg Ala Gly Val Val Leu Val Thr 280 285 290 295	963
gct gcc ggc aac ttc cgg gac gat gcc tgc ctc tac tcc cca gcc tca Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser 300 305 310	1011
gct ccc gag gtc atc aca gtt ggg gcc acc aat gcc cag gac cag ccg Ala Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Gln Asp Gln Pro 315 320 325	1059
gtg acc ctg ggg act ttg ggg acc aac ttt ggc cgc tgt gtg gac ctc Val Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu 330 335 340	1107

ttt gcc cca ggg gag gac atc att ggt gcc tcc agc gac tgc agc acc	1155
Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Thr	
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tgc ttt gtg tca cag agt ggg aca tca cag gct gct gcc cac gtg gct	1203
Cys Phe Val Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala	
360 365 370 375	
ggg tgg cag ctg ttt tgc agg act gtg tgg tca gca cac tcg ggg cct	1251
Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His Ser Gly Pro	
380 385 390	
aca cgg atg gcc aca gcc atc gcc cgc tgc gcc cca gat gag gag ctg	1299
Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp Glu Glu Leu	
395 400 405	
ctg agc tgc tcc agt ttc tcc agg agt ggg aag cgg cgg ggc gag cgc	1347
Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg Gly Glu Arg	
410 415 420	
atg gag gcc caa ggg ggc aag ctg gtc tgc cgg gcc cac aac gct ttt	1395
Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His Asn Ala Phe	
425 430 435	
ggg ggt gag ggt gtc tac gcc att gcc agg tgc tgc ctg cta ccc cag	1443
Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro Gln	
440 445 450 455	
gcc aac tgc agc gtc cac aca gct cca cca gct gag gcc agc atg ggg	1491
Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala Ser Met Gly	
460 465 470	
acc cgt gtc cac tgc cac caa cag ggc cac gtc ctc aca ggc tgc agc	1539
Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr Gly Cys Ser	
475 480 485	
tcc cac tgg gag gtg gag gac ctt ggc acc cac aag ccg cct gtg ctg	1587
Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro Pro Val Leu	
490 495 500	
agg cca cga ggt cag ccc aac cag tgc gtg ggc cac agg gag gcc agc	1635
Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg Glu Ala Ser	
505 510 515	
atc cac gct tcc tgc tgc cat gcc cca ggt ctg gaa tgc aaa gtc aag	1683
Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys Val Lys	
520 525 530 535	
gag cat gga atc ccg gcc cct cag gag cag gtg acc gtg gcc tgc gag	1731
Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val Ala Cys Glu	
540 545 550	

gag ggc tgg acc ctg act ggc tgc agt gcc ctc cct ggg acc tcc cac 1779
 Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly Thr Ser His
 555 560 565

gtc ctg ggg gcc tac gcc gta gac aac acg tgt gta gtc agg agc cgg 1827
 Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val Arg Ser Arg
 570 575 580

gac gtc agc act aca ggc agc acc agc gaa ggg gcc gtg aca gcc gtt 1875
 Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Gly Ala Val Thr Ala Val
 585 590 595

gcc atc tgc tgc cgg agc cgg cac ctg gcg cag gcc tcc cag gag ctc 1923
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 Gln

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 <212> PRT
 <213> Homo sapiens

<400> 34

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Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
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Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
 35 40 45

His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 50 55 60

Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
 65 70 75

Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 80 85 90

His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
 95 100 105 110

Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
 115 120 125

Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
 130 135 140

Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly
 145 150 155

Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
 160 165 170

His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val
 175 180 185 190

Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
 195 200 205

Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
 210 215 220

Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln
 225 230 235

Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
 240 245 250

Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
 255 260 265 270

Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu
 275 280 285

Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
 290 295 300

Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
 305 310 315

Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
 320 325 330

Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
 335 340 345 350

Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly
 355 360 365

Thr Ser Gln Ala Ala Ala His Val Ala Gly Trp Gln Leu Phe Cys Arg
 370 375 380

Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Met Ala Thr Ala Ile
 385 390 395

Ala Arg Cys Ala Pro Asp Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser
 400 405 410

Arg Ser Gly Lys Arg Arg Gly Glu Arg Met Glu Ala Gln Gly Gly Lys
 415 420 425 430

Leu Val Cys Arg Ala His Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala
 435 440 445

Ile Ala Arg Cys Cys Leu Leu Pro Gln Ala Asn Cys Ser Val His Thr
 450 455 460

Ala Pro Pro Ala Glu Ala Ser Met Gly Thr Arg Val His Cys His Gln
 465 470 475

Gln Gly His Val Leu Thr Gly Cys Ser Ser His Trp Glu Val Glu Asp
 480 485 490

Leu Gly Thr His Lys Pro Pro Val Leu Arg Pro Arg Gly Gln Pro Asn
 495 500 505 510

Gln Cys Val Gly His Arg Glu Ala Ser Ile His Ala Ser Cys Cys His
 515 520 525

Ala Pro Gly Leu Glu Cys Lys Val Lys Glu His Gly Ile Pro Ala Pro
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Gln Glu Gln Val Thr Val Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly
545 550 555

Cys Ser Ala Leu Pro Gly Thr Ser His Val Leu Gly Ala Tyr Ala Val
560 565 570

Asp Asn Thr Cys Val Val Arg Ser Arg Asp Val Ser Thr Thr Gly Ser
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                                         -25
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Ala Glu Ser Gly Leu Ala Met Trp Pro Ser Leu Leu Leu Leu Leu Leu
-20 -15 -10

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 Leu Pro Gly Pro Pro Pro Val Ala Gly Leu Glu Asp Ala Ala Phe Pro
 -5 -1 1 5

cac ctg ggg gag agc ttg cag ccc ctg ccc cgg gcc tgt ccc ctg cgc	200
His Leu Gly Glu Ser Leu Gln Pro Leu Pro Arg Ala Cys Pro Leu Arg	
10 15 20	
tgc tcc tgc ccc cga gtc gac act gtg gac tgt gat ggc ttg gac ctt	248
Cys Ser Cys Pro Arg Val Asp Thr Val Asp Cys Asp Gly Leu Asp Leu	
25 30 35 40	
cga gtg ttc ccg gac aac atc acc aga gcc gct cag cac ctc tcc ctg	296
Arg Val Phe Pro Asp Asn Ile Thr Arg Ala Ala Gln His Leu Ser Leu	
45 50 55	
cag aac aac cag ctc cag gaa ctc ccc tac aat gag ctg tcc cgc ctc	344
Gln Asn Asn Gln Leu Gln Glu Leu Pro Tyr Asn Glu Leu Ser Arg Leu	
60 65 70	
agt ggc ctg cga acc ctc aac ctc cac aac aac ctc atc ttc tcc gaa	392
Ser Gly Leu Arg Thr Leu Asn Leu His Asn Asn Leu Ile Phe Ser Glu	
75 80 85	
ggc ctg cct gac gag gcc ttc gag tcc ctc acc cag ctg cag cac ctc	440
Gly Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His Leu	
90 95 100	
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Cys Val Ala His Asn Lys Leu Ser Asn Ala Gly Leu Pro Pro Asp Ala	
105 110 115 120	
ttc cgc ggc tcc gag gcc atc gcc acc ctc agc ctc tcc aac aac cag	536
Phe Arg Gly Ser Glu Ala Ile Ala Thr Leu Ser Leu Ser Asn Asn Gln	
125 130 135	
ctc agc tac ctg ccg ccc agc ctg ccg ccc tca ctc gag cgg ctc cac	584
Leu Ser Tyr Leu Pro Pro Ser Leu Pro Pro Ser Leu Glu Arg Leu His	
140 145 150	
ctg cag aac aat ctc atc tcc aag gtg ccc cga gga gcc ctg agc cgc	632
Leu Gln Asn Asn Leu Ile Ser Lys Val Pro Arg Gly Ala Leu Ser Arg	
155 160 165	
cag act caa ctc cgt gag ctc tac ctc cag cac aac cag ctg aca gac	680
Gln Thr Gln Leu Arg Glu Leu Tyr Leu Gln His Asn Gln Leu Thr Asp	
170 175 180	
agt ggc ctg gat gcc acc acc ttc agc aag ctg cat agc ctt gaa tac	728
Ser Gly Leu Asp Ala Thr Thr Phe Ser Lys Leu His Ser Leu Glu Tyr	
185 190 195 200	
ctg gat ctc tcc cac aac cag ctg acc aca gtg ccc gcc ggc ctg ccc	776
Leu Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Ala Gly Leu Pro	
205 210 215	

cgg acc ctg gct atc ctg cac ctg ggc cgc aac cgc atc cgg cag gtg Arg Thr Leu Ala Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln Val 220 225 230	824
gag gcg gct cgg ctg cac ggg gcg cgt ggt ctg cgc tat ttg ttg ctg Glu Ala Ala Arg Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Leu 235 240 245	872
cag cac aac cag ctg ggg agc tca ggg ctg ccc gcc ggg gct ctg cgg Gln His Asn Gln Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg 250 255 260	920
ccg ctg cgg ggc ctg cac acg ctg cac ctc tat ggc aat ggg ctg gac Pro Leu Arg Gly Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp 265 270 275 280	968
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(19) World Intellectual Property Organization
International Bureau



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(22) International Filing Date: **30 July 2001 (30.07.2001)**

(25) Filing Language: **English**

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(30) Priority Data:

60/224,642 11 August 2000 (11.08.2000) US
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

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(72) Inventors; and

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(74) Agents: **DAVIS, Paula, K.** et al.; Eli Lilly and Company, Lilly Corporate Center, DC 1104, Indianapolis, IN 46285 (US).

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(88) Date of publication of the international search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **NOVEL SECRETED PROTEINS AND THEIR USES**

(57) Abstract: The present invention provides nucleic acid sequences encoding novel human proteins. These novel nucleic acids are useful for constructing the claimed DNA vectors and host cells of the invention and for preparing the claimed nucleic acids, recombinant proteins and antibodies that are useful in the claimed methods and medical uses.



WO 02/014358 A3

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21124

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/62 C12N5/10 C12N1/21 C07K14/47
C07K14/475 C07K16/18 A61K39/395 A61K31/713 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBL, EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 29718 A (GENETICS INST) 17 June 1999 (1999-06-17) cited in the application the whole document ---	1-21
X	US 5 916 751 A (TABIBZADEH SIAMAK ET AL) 29 June 1999 (1999-06-29) the whole document ---	1-21
X	WO 99 09198 A (HUMAN GENOME SCIENCES INC ;EBNER REINHARD (US); RUBEN STEVEN M (US) 25 February 1999 (1999-02-25) cited in the application the whole document ---	1-21
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 August 2002

Date of mailing of the international search report

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Name and mailing address of the ISA

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Authorized officer

Aslund, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/21124

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 06443 A (HUYNH THANH V ;LEE SE JIN (US); SEBALD SUZANNE (US); UNIV JOHNS HO) 11 February 1999 (1999-02-11) the whole document ---	1-21
X	KOSAKI K ET AL: "Characterization and mutation analysis of human LEFTY A and LEFTY B, homologues of murine genes implicated in left-right axis development." AMERICAN JOURNAL OF HUMAN GENETICS, vol. 64, no. 3, March 1999 (1999-03), pages 712-721, XP002210149 ISSN: 0002-9297 cited in the application figure 3A ---	1-10
P,X	WO 00 66068 A (NORTH SHORE LONG ISLAND JEWISH) 9 November 2000 (2000-11-09) the whole document -----	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/21124

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: **17(partially), 18 (partially), 19**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-21 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-21 (all partially)

A nucleic acid of SEQ ID No 1 encoding the polypeptide LP105 of Seq Id No 2.

Furthermore, vectors expressing said polypeptide and derivatives, transformed host cells, antibodies and pharmaceutical compositions comprising said nucleic acid/ polypeptide or antibodies directed to said polypeptide.

Invention 2-19: Claims 1-21 (all partially)

As for invention 1, but relating to nucleic acids of the following SEQ ID NOs and the encoded polypeptides of the following Seq Id NOs.

Nucleic acid SEQ ID NOs:	Polypeptide Seq Id NOs
3	4
5	6
7	8
9	10
11	12
13	14
15	16
17	18
19	20
21	22
23	24
25	26
27	28
29	30
31	32
33	34
35	36
37	38

Furthermore, vectors expressing said polypeptide and derivatives, transformed host cells, antibodies and pharmaceutical compositions comprising said nucleic acid/ polypeptide or antibodies directed to said polypeptide.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17(partially), 18 (partially), 19

Present claims 17 (partially), 18 (partially), 19 relate to compounds defined by reference to a desirable characteristic or property, namely the ability to have an agonistic or antagonistic effect on the polypeptide of SEQ ID 2. The claims cover all amounts of composition and all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT only for antibodies directed to the polypeptide of SEQ ID 2. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for claims 17, 18 and 19 only for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to an LP polypeptide, an LP polypeptide antibody, an anti-LP polypeptide ribozyme, a polynucleotide encoding the LP polypeptide of SEQ ID 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/21124

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